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(71) Applicant: **AMGEN INC.**
Amgen Center,
1840 Dehavilland Drive
Thousand Oaks, CA 91320-1789 (US)

(72) Inventor: **Osslund, Timothy**
475 Vista Montana
Camarillo, California 93010 (US)

(74) Representative: **Vossius, Volker, Dr. et al**
Dr. Volker Vossius
Patentanwaltskanzlei - Rechtsanwaltskanzlei
Holbeinstrasse 5
D-81679 München (DE)

(54) **G-CSF analog compositions and methods.**

(57) Provided herein are granulocyte colony stimulating factor ("G-CSF") analogs, compositions containing such analogs, and related compositions. In another aspect, provided herein are nucleic acids encoding the present analogs or related nucleic acids, related host cells and vectors. In yet another aspect, provided herein are computer programs and apparatuses for expressing the three dimensional structure of G-CSF and analogs thereof. In another aspect, provided herein are methods for rationally designing G-CSF analogs and related compositions. In yet another aspect, provided herein are methods for treatment using the present G-CSF analogs.

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Field of the Invention

This invention relates to granulocyte colony stimulating factor ("G-CSF") analogs, compositions containing such analogs, and related compositions. In another aspect, the present invention relates to nucleic acids encoding the present analogs or related nucleic acids, related host cells and vectors. In another aspect, the invention relates to computer programs and apparatuses for expressing the three dimensional structure of G-CSF and analogs thereof. In another aspect, the invention relates to methods for rationally designing G-CSF analogs and related compositions. In yet another aspect, the present invention relates to methods for treatment using the present G-CSF analogs.

Background

Hematopoiesis is controlled by two systems: the cells within the bone marrow microenvironment and growth factors. The growth factors, also called colony stimulating factors, stimulate committed progenitor cells to proliferate and to form colonies of differentiating blood cells. One of these factors is granulocyte colony stimulating factor, herein called G-CSF, which preferentially stimulates the growth and development of neutrophils, indicating a potential use in neutropenic states. Welte et al., PNAS-USA 82: 1526-1530 (1985); Souza et al., Science 232: 61-65 (1986) and Gabrilove, J. Seminars in Hematology 26: (2) 1-14 (1989).

In humans, endogenous G-CSF is detectable in blood plasma. Jones et al., Bailliere's Clinical Hematology 2 (1): 83-111 (1989). G-CSF is produced by fibroblasts, macrophages, T cells trophoblasts, endothelial cells and epithelial cells and is the expression product of a single copy gene comprised of four exons and five introns located on chromosome seventeen. Transcription of this locus produces a mRNA species which is differentially processed, resulting in two forms of G-CSF mRNA, one version coding for a protein of 177 amino acids, the other coding for a protein of 174 amino acids, Nagata et al., EMBO J 5: 575-581 (1986), and the form comprised of 174 amino acids has been found to have the greatest specific in vivo biological activity. G-CSF is species cross-reactive, such that when human G-CSF is administered to another mammal such as a mouse, canine or monkey, sustained neutrophil leukocytosis is elicited. Moore et al., PNAS-USA 84: 7134-7138 (1987).

Human G-CSF can be obtained and purified from a number of sources. Natural human G-CSF (nhG-CSF) can be isolated from the supernatants of cultured human tumor cell lines. The development of recombinant DNA technology, see, for instance, U.S. Patent 4,810,643 (Souza) incorporated herein by reference, has enabled the production of commercial scale quantities of G-CSF in glycosylated form as a product of eukaryotic host cell expression, and of G-CSF in non-glycosylated form as a product of prokaryotic host cell expression.

G-CSF has been found to be useful in the treatment of indications where an increase in neutrophils will provide benefits. For example, for cancer patients, G-CSF is beneficial as a means of selectively stimulating neutrophil production to compensate for hematopoietic deficits resulting from chemotherapy or radiation therapy. Other indications include treatment of various infectious diseases and related conditions, such as sepsis, which is typically caused by a metabolite of bacteria. G-CSF is also useful alone, or in combination with other compounds, such as other cytokines, for growth or expansion of cells in culture, for example, for bone marrow transplants.

Signal transduction, the way in which G-CSF effects cellular metabolism, is not currently thoroughly understood. G-CSF binds to a cell-surface receptor which apparently initiates the changes within particular progenitor cells, leading to cell differentiation.

Various altered G-CSF's have been reported. Generally, for design of drugs, certain changes are known to have certain structural effects. For example, deleting one cysteine could result in the unfolding of a molecule which is, in its unaltered state, is normally folded via a disulfide bridge. There are other known methods for adding, deleting or substituting amino acids in order to change the function of a protein.

Recombinant human G-CSF mutants have been prepared, but the method of preparation does not include overall structure/function relationship information. For example, the mutation and biochemical modification of Cys 18 has been reported. Kuga et al., Biochem. Biophy. Res. Comm 159: 103-111 (1989); Lu et al., Arch. Biochem. Biophys. 268: 81-92 (1989).

In U.S. Patent No. 4, 810, 643, entitled, "Production of Pluripotent Granulocyte Colony-Stimulating Factor" (as cited above), polypeptide analogs and peptide fragments of G-CSF are disclosed generally. Specific G-CSF analogs disclosed include those with the cysteins at positions 17, 36, 42, 64, and 74 (of the 174 amino acid species or of those having 175 amino acids, the additional amino acid being an N-terminal methionine) substituted with another amino acid, (such as serine), and G-CSF with an alanine in the first (N-

terminal) position.

EP 0 335 423 entitled "Modified human G-CSF" reportedly discloses the modification of at least one amino group in a polypeptide having hG-CSF activity.

EP 0 272 703 entitled "Novel Polypeptide" reportedly discloses G-CSF derivatives having an amino acid substituted or deleted at or "in the neighborhood" of the N terminus.

EP 0 459 630, entitled "Polypeptides" reportedly discloses derivatives of naturally occurring G-CSF having at least one of the biological properties of naturally occurring G-CSF and a solution stability of at least 35% at 5 mg/ml in which the derivative has at least Cys^{17} of the native sequence replaced by a Ser^{17} residue and Asp^{27} of the native sequence replaced by a Ser^{27} residue.

EP 0 256 843 entitled "Expression of G-CSF and Muteins Thereof and Their Uses" reportedly discloses a modified DNA sequence encoding G-CSF wherein the N-terminus is modified for enhanced expression of protein in recombinant host cells, without changing the amino acid sequence of the protein.

EP 0 243 153 entitled "Human G-CSF Protein Expression" reportedly discloses G-CSF to be modified by inactivating at least one yeast KEX2 protease processing site for increased yield in recombinant production using yeast.

Shaw, U.S. Patent No. 4,904,584, entitled "Site-Specific Homogeneous Modification of Polypeptides," reportedly discloses lysine altered proteins.

WO/9012874 reportedly discloses cysteine altered variants of proteins.

Australian patent application Document No. AU-A-10948/92, entitled, "Improved Activation of Recombinant Proteins" reportedly discloses the addition of amino acids to either terminus of a G-CSF molecule for the purpose of aiding in the folding of the molecule after prokaryotic expression.

Australian patent application Document No. AU-A-76380/91, entitled, "Muteins of the Granulocyte Colony Stimulating Factor (G-CSF)" reportedly discloses muteins of the granulocyte stimulating factor G-CSF in the sequence Leu-Gly-His-Ser-Leu-Gly-Ile at position 50-56 of G-CSF with 174 amino acids, and position 53 to 59 of the G-CSF with 177 amino acids, or/and at least one of the four histadine residues at positions 43, 79, 156 and 170 of the mature G-CSF with 174 amino acids or at positions 46, 82, 159, or 173 of the mature G-CSF with 177 amino acids.

GB 2 213 821, entitled "Synthetic Human Granulocyte Colony Stimulating Factor Gene" reportedly discloses a synthetic G-CSF-encoding nucleic acid sequence incorporating restriction sites to facilitate the cassette mutagenesis of selected regions, and flanking restriction sites to facilitate the incorporation of the gene into a desired expression system.

G-CSF has reportedly been crystallized to some extent, e.g., EP 344 796, and the overall structure of G-CSF has been surmised, but only on a gross level. Bazan, Immunology Today 11: 350-354 (1990); Parry et al., J. Molecular Recognition 8: 107-110 (1988). To date, there have been no reports of the overall structure of G-CSF, and no systematic studies of the relationship of the overall structure and function of the molecule, studies which are essential to the systematic design of G-CSF analogs. Accordingly, there exists a need for a method of this systematic design of G-CSF analogs, and the resultant compositions.

Summary of the Invention

The three dimensional structure of G-CSF has now been determined to the atomic level. From this three-dimensional structure, one can now forecast with substantial certainty how changes in the composition of a G-CSF molecule may result in structural changes. These structural characteristics may be correlated with biological activity to design and produce G-CSF analogs.

Although others had speculated regarding the three dimensional structure of G-CSF, Bazan, Immunology Today 11: 350-354 (1990); Parry et al., J. Molecular Recognition 8: 107-110 (1988), these speculations were of no help to those wishing to prepare G-CSF analogs either because the surmised structure was incorrect (Parry et al., supra) and/or because the surmised structure provided no detail correlating the constituent moieties with structure. The present determination of the three-dimensional structure to the atomic level is by far the most complete analysis to date, and provides important information to those wishing to design and prepare G-CSF analogs. For example, from the present three dimensional structural analysis, precise areas of hydrophobicity and hydrophilicity have been determined.

Relative hydrophobicity is important because it directly relates to the stability of the molecule. Generally, biological molecules, found in aqueous environments, are externally hydrophilic and internally hydrophobic; in accordance with the second law of thermodynamics provides, this is the lowest energy state and provides for stability. Although one could have speculated that G-CSF's internal core would be hydrophobic, and the outer areas would be hydrophilic, one would have had no way of knowing specific hydrophobic or hydrophilic areas. With the presently provided knowledge of areas of hydrophobic-

ity/philicity, one may forecast with substantial certainty which changes to the G-CSF molecule will affect the overall structure of the molecule.

As a general rule, one may use knowledge of the geography of the hydrophobic and hydrophilic regions to design analogs in which the overall G-CSF structure is not changed, but change does affect biological activity ("biological activity" being used here in its broadest sense to denote function). One may correlate biological activity to structure. If the structure is not changed, and the mutation has no effect on biological activity, then the mutation has no biological function. If, however, the structure is not changed and the mutation does affect biological activity, then the residue (or atom) is essential to at least one biological function. Some of the present working examples were designed to provide no change in overall structure, yet have a change in biological function.

Based on the correlation of structure to biological activity, one aspect of the present invention relates to G-CSF analogs. These analogs are molecules which have more, fewer, different or modified amino acid residues from the G-CSF amino acid sequence. The modifications may be by addition, substitution, or deletion of one or more amino acid residues. The modification may include the addition or substitution of analogs of the amino acids themselves, such as peptidomimetics or amino acids with altered moieties such as altered side groups. The G-CSF used as a basis for comparison may be of human, animal or recombinant nucleic acid-technology origin (although the working examples disclosed herein are based on the recombinant production of the 174 amino acid species of human G-CSF, having an extra N-terminus methionyl residue). The analogs may possess functions different from natural human G-CSF molecule, or may exhibit the same functions, or varying degrees of the same functions. For example, the analogs may be designed to have a higher or lower biological activity, have a longer shelf-life or a decrease in stability, be easier to formulate, or more difficult to combine with other ingredients. The analogs may have no hematopoietic activity, and may therefore be useful as an antagonist against G-CSF effect (as, for example, in the overproduction of G-CSF). From time to time herein the present analogs are referred to as proteins or peptides for convenience, but contemplated herein are other types of molecules, such as peptidomimetics or chemically modified peptides.

In another aspect, the present invention relates to related compositions containing a G-CSF analog as an active ingredient. The term, "related composition," as used herein, is meant to denote a composition which may be obtained once the identity of the G-CSF analog is ascertained (such as a G-CSF analog labeled with a detectable label, related receptor or pharmaceutical composition). Also considered a related composition are chemically modified versions of the G-CSF analog, such as those having attached at least one polyethylene glycol molecule.

For example, one may prepare a G-CSF analog to which a detectable label is attached, such as a fluorescent, chemiluminescent or radioactive molecule.

Another example is a pharmaceutical composition which may be formulated by known techniques using known materials, see, e.g., Remington's Pharmaceutical Sciences, 18th Ed. (1990, Mack Publishing Co., Easton, Pennsylvania 18042) pages 1435-1712, which are herein incorporated by reference. Generally, the formulation will depend on a variety of factors such as administration, stability, production concerns and other factors. The G-CSF analog may be administered by injection or by pulmonary administration via inhalation. Enteric dosage forms may also be available for the present G-CSF analog compositions, and therefore oral administration may be effective. G-CSF analogs may be inserted into liposomes or other microcarriers for delivery, and may be formulated in gels or other compositions for sustained release. Although preferred compositions will vary depending on the use to which the composition will be put, generally, for G-CSF analogs having at least one of the biological activities of natural G-CSF, preferred pharmaceutical compositions are those prepared for subcutaneous injection or for pulmonary administration via inhalation, although the particular formulations for each type of administration will depend on the characteristics of the analog.

Another example of related composition is a receptor for the present analog. As used herein, the term "receptor" indicates a moiety which selectively binds to the present analog molecule. For example, antibodies, or fragments thereof, or "recombinant antibodies" (see Huse et al., Science 246:1275 (1989)) may be used as receptors. Selective binding does not mean only specific binding (although binding-specific receptors are encompassed herein), but rather that the binding is not a random event. Receptors may be on the cell surface or intra- or extra-cellular, and may act to effectuate, inhibit or localize the biological activity of the present analogs. Receptor binding may also be a triggering mechanism for a cascade of activity indirectly related to the analog itself. Also contemplated herein are nucleic acids, vectors containing such nucleic acids and host cells containing such nucleic acids which encode such receptors.

Another example of a related composition is a G-CSF analog with a chemical moiety attached. Generally, chemical modification may alter biological activity or antigenicity of a protein, or may alter other

characteristics, and these factors will be taken into account by a skilled practitioner. As noted above, one example of such chemical moiety is polyethylene glycol. Modification may include the addition of one or more hydrophilic or hydrophobic polymer molecules, fatty acid molecules, or polysaccharide molecules. Examples of chemical modifiers include polyethylene glycol, alkIpolyethylene glycols, DI-poly(amino acids), polyvinylpyrrolidone, polyvinyl alcohol, pyran copolymer, acetic acid/acylation, proprionic acid, palmitic acid, stearic acid, dextran, carboxymethyl cellulose, pullulan, or agarose. See, Francis, *Focus on Growth Factors* 3: 4-10 (May 1992) (published by Mediscript, Mountview Court, Friern Barnet Lane, London N20 OLD, UK). Also, chemical modification may include an additional protein or portion thereof, use of a cytotoxic agent, or an antibody. The chemical modification may also include lecithin.

In another aspect, the present invention relates to nucleic acids encoding such analogs. The nucleic acids may be DNAs or RNAs or derivatives thereof, and will typically be cloned and expressed on a vector, such as a phage or plasmid containing appropriate regulatory sequences. The nucleic acids may be labeled (such as using a radioactive, chemiluminescent, or fluorescent label) for diagnostic or prognostic purposes, for example. The nucleic acid sequence may be optimized for expression, such as including codons preferred for bacterial expression. The nucleic acid and its complementary strand, and modifications thereof which do not prevent encoooding of the desired analog are here contemplated.

In another aspect, the present invention relates to host cells containing the above nucleic acids encoding the present analogs. Host cells may be eukaryotic or prokaryotic, and expression systems may include extra steps relating to the attachment (or prevention) of sugar groups (glycosylation), proper folding of the molecule, the addition or deletion of leader sequences or other factors incident to recombinant expression.

In another aspect the present invention relates to antisense nucleic acids which act to prevent or modify the type or amount of expression of such nucleic acid sequences. These may be prepared by known methods.

In another aspect of the present invention, the nucleic acids encoding a present analog may be used for gene therapy purposes, for example, by placing a vector containing the analog-encoding sequence into a recipient so the nucleic acid itself is expressed inside the recipient who is in need of the analog composition. The vector may first be placed in a carrier, such as a cell, and then the carrier placed into the recipient. Such expression may be localized or systemic. Other carriers include non-naturally occurring carriers, such as liposomes or other microcarriers or particles, which may act to mediate gene transfer into a recipient.

The present invention also provides for computer programs for the expression (such as visual display) of the G-CSF or analog three dimensional structure, and further, a computer program which expresses the identity of each constituent of a G-CSF molecule and the precise location within the overall structure of that constituent, down to the atomic level. Set forth below is one example of such program. There are many currently available computer programs for the expression of the three dimensional structure of a molecule. Generally, these programs provide for inputting of the coordinates for the three dimensional structure of a molecule (i.e., for example, a numerical assignment for each atom of a G-CSF molecule along an x, y, and z axis), means to express (such as visually display) such coordinates, means to alter such coordinates and means to express an image of a molecule having such altered coordinates. One may program crystallographic information, i.e., the coordinates of the location of the atoms of a G-CSF molecule in three dimension space, wherein such coordinates have been obtained from crystallographic analysis of said G-CSF molecule, into such programs to generate a computer program for the expression (such as visual display) of the G-CSF three dimensional structure. Also provided, therefore, is a computer program for the expression of G-CSF analog three dimensional structure. Preferred is the computer program Insight II, version 4, available from Biosym, San Diego, California, with the coordinates as set forth in FIGURE 5 input. Preferred expression means is on a Silicon Graphics 320 VGX computer, with Crystal Eyes glasses (also available from Silicon Graphics), which allows one to view the G-CSF molecule or its analog stereoscopically. Alternatively, the present G-CSF crystallographic coordinates and diffraction data are also deposited in the Protein Data Bank, Chemistry Department, Brookhaven National Laboratory, Upton, New York 119723, USA. One may use these data in preparing a different computer program for expression of the three dimensional structure of a G-CSF molecule or analog thereof. Therefore, another aspect of the present invention is a computer program for the expression of the three dimensional structure of a G-CSF molecule. Also provided is said computer program for visual display of the three dimensional structure of a G-CSF molecule; and further, said program having means for altering such visual display. Apparatus useful for expression of such computer program, particularly for the visual display of the computer image of said three dimensional structure of a G-CSF molecule or analog thereof is also therefore here provided, as well as means for preparing said computer program and apparatus.

The computer program is useful for preparation of G-CSF analogs because one may select specific sites on the G-CSF molecule for alteration and readily ascertain the effect the alteration will have on the overall structure of the G-CSF molecule. Selection of said site for alteration will depend on the desired biological characteristic of the G-CSF analog. If one were to randomly change said G-CSF molecule (r-met-hu-G-CSF) there would be 175^{20} possible substitutions, and even more analogs having multiple changes, additions or deletions. By viewing the three dimensional structure wherein said structure is correlated with the composition of the molecule, the selection for sites of alteration is no longer a random event, but sites for alteration may be determined rationally.

As set forth above, identity of the three dimensional structure of G-CSF, including the placement of each constituent down to the atomic level has now yielded information regarding which moieties are necessary to maintain the overall structure of the G-CSF molecule. One may therefore select whether to maintain the overall structure of the G-CSF molecule when preparing a G-CSF analog of the present invention, or whether (and how) to change the overall structure of the G-CSF molecule when preparing a G-CSF analog of the present invention. Optionally, once one has prepared such analog, one may test such analog for a desired characteristic.

One may, for example, seek to maintain the overall structure possessed by a non-altered natural or recombinant G-CSF molecule. The overall structure is presented in Figures 2, 3, and 4, and is described in more detail below. Maintenance of the overall structure may ensure receptor binding, a necessary characteristic for an analog possessing the hematopoietic capabilities of natural G-CSF (if no receptor binding, signal transduction does not result from the presence of the analog). It is contemplated that one class of G-CSF analogs will possess the three dimensional core structure of a natural or recombinant (non-altered) G-CSF molecule, yet possess different characteristics, such as an increased ability to selectively stimulate neutrophils. Another class of G-CSF analogs are those with a different overall structure which diminishes the ability of a G-CSF analog molecule to bind to a G-CSF receptor, and possesses a diminished ability to selectively stimulate neutrophils as compared to non-altered natural or recombinant G-CSF.

For example, it is now known which moieties within the internal regions of the G-CSF molecule are hydrophobic, and, correspondingly, which moieties on the external portion of the G-CSF molecule are hydrophilic. Without knowledge of the overall three dimensional structure, preferably to the atomic level as provided herein, one could not forecast which alterations within this hydrophobic internal area would result in a change in the overall structural conformation of the molecule. An overall structural change could result in a functional change, such as lack of receptor binding, for example, and therefore, diminishment of biological activity as found in non-altered G-CSF. Another class of G-CSF analogs is therefore G-CSF analogs which possess the same hydrophobicity as (non-altered) natural or recombinant G-CSF. More particularly, another class of G-CSF analogs possesses the same hydrophobic moieties within the four helical bundle of its internal core as those hydrophobic moieties possessed by (non-altered) natural or recombinant G-CSF yet have a composition different from said non-altered natural or recombinant G-CSF.

Another example relates to external loops which are structures which connect the internal core (helices) of the G-CSF molecule. From the three dimensional structure -- including information regarding the spatial location of the amino acid residues -- one may forecast that certain changes in certain loops will not result in overall conformational changes. Therefore, another class of G-CSF analogs provided herein is that having an altered external loop but possessing the same overall structure as (non-altered) natural or recombinant G-CSF. More particularly, another class of G-CSF analogs provided herein are those having an altered external loop, said loop being selected from the loop present between helices A and B; between helices B and C; between helices C and D; between helices D and A, as those loops and helices are identified herein. More particularly, said loops, preferably the AB loop and/or the CD loop are altered to increase the half life of the molecule by stabilizing said loops. Such stabilization may be by connecting all or a portion of said loop(s) to a portion of an alpha helical bundle found in the core of a G-CSF (or analog) molecule. Such connection may be via beta sheet, salt bridge, disulfide bonds, hydrophobic interaction or other connecting means available to those skilled in the art, wherein such connecting means serves to stabilize said external loop or loops. For example, one may stabilize the AB or CD loops by connecting the AB loop to one of the helices within the internal region of the molecule.

The N-terminus also may be altered without change in the overall structure of a G-CSF molecule, because the N-terminus does not effect structural stability of the internal helices, and, although the external loops are preferred for modification, the same general statements apply to the N-terminus.

Additionally, such external loops may be the site(s) for chemical modification because in (non-altered) natural or recombinant G-CSF such loops are relatively flexible and tend not to interfere with receptor binding. Thus, there would be additional room for a chemical moiety to be directly attached (or indirectly

attached via another chemical moiety which serves as a chemical connecting means). The chemical moiety may be selected from a variety of moieties available for modification of one or more function of a G-CSF molecule. For example, an external loop may provide sites for the addition of one or more polymer which serves to increase serum half-life, such as a polyethylene glycol molecule. Such polyethylene glycol molecule(s) may be added wherein said loop is altered to include additional lysines which have reactive side groups to which polyethylene glycol moieties are capable of attaching. Other classes of chemical moieties may also be attached to one or more external loops, including but not limited to other biologically active molecules, such as receptors, other therapeutic proteins (such as other hematopoietic factors which would engender a hybrid molecule), or cytotoxic agents (such as diphtheria toxin). This list is of course not complete; one skilled in the art possessed of the desired chemical moiety will have the means to effect attachment of said desired moiety to the desired external loop. Therefore, another class of the present G-CSF analogs includes those with at least one alteration in an external loop wherein said alteration provides for the addition of a chemical moiety such as at least one polyethylene glycol molecule.

Deletions, such as deletions of sites recognized by proteins for degradation of the molecule, may also be effectual in the external loops. This provides alternative means for increasing half-life of a molecule otherwise having the G-CSF receptor binding and signal transduction capabilities (i.e., the ability to selectively stimulate the maturation of neutrophils). Therefore, another class of the present G-CSF analogs includes those with at least one alteration in an external loop wherein said alteration decreases the turnover of said analog by proteases. Preferred loops for such alterations are the AB loop and the CD loop. One may prepare an abbreviated G-CSF molecule by deleting a portion of the amino acid residues found in the external loops (identified in more detail below), said abbreviated G-CSF molecule may have additional advantages in preparation or in biological function.

Another example relates to the relative charges between amino acid residues which are in proximity to each other. As noted above, the G-CSF molecule contains a relatively tightly packed four helical bundle. Some of the faces on the helices face other helices. At the point (such as a residue) where a helix faces another helix, the two amino acid moieties which face each other may have the same charge, and thus tend to repel each other, which lends instability to the overall molecule. This may be eliminated by changing the charge (to an opposite charge or a neutral charge) of one or both of the amino acid moieties so that there is no repelling. Therefore, another class of G-CSF analogs includes those G-CSF analogs having been altered to modify instability due to surface interactions, such as electron charge location.

In another aspect, the present invention relates to methods for designing G-CSF analogs and related compositions and the products of those methods. The end products of the methods may be the G-CSF analogs as defined above or related compositions. For instance, the examples disclosed herein demonstrate (a) the effects of changes in the constituents (i.e., chemical moieties) of the G-CSF molecule on the G-CSF structure and (b) the effects of changes in structure on biological function. Essentially, therefore, another aspect of the present invention is a method for preparing a G-CSF analog comprising the steps of:

(a) viewing information conveying the three dimensional structure of a G-CSF molecule wherein the chemical moieties, such as each amino acid residue or each atom of each amino acid residue, of the G-CSF molecule are correlated with said structure;

(b) selecting from said information a site on a G-CSF molecule for alteration;

(c) preparing a G-CSF analog molecule having such alteration; and

(d) optionally, testing such G-CSF analog molecule for a desired characteristic.

One may use the here provided computer programs for a computer-based method for preparing a G-CSF analog. Another aspect of the present invention is therefore a computer based method for preparing a G-CSF analog comprising the steps of:

(a) providing computer expression of the three dimensional structure of a G-CSF molecule wherein the chemical moieties, such as each amino acid residue or each atom of each amino acid residue, of the G-CSF molecule are correlated with said structure;

(b) selecting from said computer expression a site on a G-CSF molecule for alteration;

(c) preparing a G-CSF molecule having such alteration; and

(d) optionally, testing such G-CSF molecule for a desired characteristic.

More specifically, the present invention provides a method for preparing a G-CSF analog comprising the steps of:

(a) viewing the three dimensional structure of a G-CSF molecule via a computer, said computer programmed (i) to express the coordinates of a G-CSF molecule in three dimensional space, and (ii) to allow for entry of information for alteration of said G-CSF expression and viewing thereof;

(b) selecting a site on said visual image of said G-CSF molecule for alteration;

(c) entering information for said alteration on said computer;

(d) viewing a three dimensional structure of said altered G-CSF molecule via said computer;
(e) optionally repeating steps (a)-(e);
(f) preparing a G-CSF analog with said alteration; and
(g) optionally testing said G-CSF analog for a desired characteristic.

In another aspect, the present invention relates to methods of using the present G-CSF analogs and related compositions and methods for the treatment or protection of mammals, either alone or in combination with other hematopoietic factors or drugs in the treatment of hematopoietic disorders. It is contemplated that one aspect of designing G-CSF analogs will be the goal of enhancing or modifying the characteristics non-modified G-CSF is known to have.

For example, the present analogs may possess enhanced or modified activities, so, where G-CSF is useful in the treatment of (for example) neutropenia, the present compositions and methods may also be of such use.

Another example is the modification of G-CSF for the purpose of interacting more effectively when used in combination with other factors particularly in the treatment of hematopoietic disorders. One example of such combination use is to use an early-acting hematopoietic factor (i.e., a factor which acts earlier in the hematopoiesis cascade on relatively undifferentiated cells) and either simultaneously or in seriatim use of a later-acting hematopoietic factor, such as G-CSF or analog thereof (as G-CSF acts on the CFU-GM lineage in the selective stimulation of neutrophils). The present methods and compositions may be useful in therapy involving such combinations or "cocktails" of hematopoietic factors.

The present compositions and methods may also be useful in the treatment of leukopenia, mylogenous leukemia, severe chronic neutropenia, aplastic anemia, glycogen storage disease, mucosistitis, and other bone marrow failure states. The present compositions and methods may also be useful in the treatment of hematopoietic deficits arising from chemotherapy or from radiation therapy. The success of bone marrow transplantation, or the use of peripheral blood progenitor cells for transplantation, for example, may be enhanced by application of the present compositions (proteins or nucleic acids for gene therapy) and methods. The present compositions and methods may also be useful in the treatment of infectious diseases, such in the context of wound healing, burn treatment, bacteremia, septicemia, fungal infections, endocarditis, osteopyelitis, infection related to abdominal trauma, infections not responding to antibiotics, pneumonia and the treatment of bacterial inflammation may also benefit from the application of the present compositions and methods. In addition, the present compositions and methods may be useful in the treatment of leukemia based upon a reported ability to differentiate leukemic cells. Welte et al., PNAS-USA 82: 1526-1530 (1985). Other applications include the treatment of individuals with tumors, using the present compositions and methods, optionally in the presence of receptors (such as antibodies) which bind to the tumor cells. For review articles on therapeutic applications, see Lieshhke and Burgess, N.Engl.J.Med. 327: 28-34 and 99-106 (1992) both of which are herein incorporated by reference.

The present compositions and methods may also be useful to act as intermediaries in the production of other moieties; for example, G-CSF has been reported to influence the production of other hematopoietic factors and this function (if ascertained) may be enhanced or modified via the present compositions and/or methods.

The compositions related to the present G-CSF analogs, such as receptors, may be useful to act as an antagonist which prevents the activity of G-CSF or an analog. One may obtain a composition with some or all of the activity of non-altered G-CSF or a G-CSF analog, and add one or more chemical moieties to alter one or more properties of such G-CSF or analog. With knowledge of the three dimensional conformation, one may forecast the best geographic location for such chemical modification to achieve the desired effect.

General objectives in chemical modification may include improved half-life (such as reduced renal, immunological or cellular clearance), altered bioactivity (such as altered enzymatic properties, dissociated bioactivities or activity in organic solvents), reduced toxicity (such as concealing toxic epitopes, compartmentalization, and selective biodistribution), altered immunoreactivity (reduced immunogenicity, reduced antigenicity or adjuvant action), or altered physical properties (such as increased solubility, improved thermal stability, improved mechanical stability, or conformational stabilization). See Francis, *Focus on Growth Factors* 3: 4-10 (May 1992) (published by Mediscript, Mountview Court, Friern Barnet Lane, London N20 OLD, UK).

The examples below are illustrative of the present invention and are not intended as a limitation. It is understood that variations and modifications will occur to those skilled in the art, and it is intended that the appended claims cover all such equivalent variations which come within the scope of the invention as claimed.

Detailed Description of the Drawings

FIGURE 1 is an illustration of the amino acid sequence of the 174 amino acid species of G-CSF with an additional N-terminal methionine (Seq. ID No.: 1) (Seq. ID No.: 2).

FIGURE 2 is an topology diagram of the crystalline structure of G-CSF, as well as hGH, pGH, GM-CSF, INF-B, IL-2, and IL-4. These illustrations are based on inspection of cited references. The length of secondary structural elements are drawn in proportion to the number of residues. A, B, C, and D helices are labeled according to the scheme used herein for G-CSF. For INF-β, the original labeling of helices is indicated in parentheses.

FIGURE 3 is an "ribbon diagram" of the three dimensional structure of G-CSF. Helix A is amino acid residues 11-39 (numbered according to Figure 1, above), helix B is amino acid residues 72-91, helix C is amino acid residues 100-123, and helix D is amino acid residues 143-173. The relatively short 3^{10} helix is at amino acid residues 45-48, and the alpha helix is at amino acid residues 48-53. Residues 93-95 form almost one turn of a left handed helix.

FIGURE 4 is a "barrel diagram" of the three dimensional structure of G-CSF. Shown in various shades of gray are the overall cylinders and their orientations for the three dimensional structure of G-CSF. The numbers indicate amino acid residue position according to FIGURE 1 above.

FIGURE 5 is a list of the coordinates used to generate a computer-aided visual image of the three-dimensional structure of G-CSF. The coordinates are set forth below. The columns correspond to separate field:

(i) Field 1 (from the left hand side) is the atom,

(ii) Field 2 is the assigned atom number,

(iii) Field 3 is the atom name (according to the periodic table standard nomenclature, with CB being carbon atom Beta, CG is Carbon atom Gamma, etc.);

(iv) Field 4 is the residue type (according to three letter nomenclature for amino acids as found in, e.g., Stryer, Biochemistry, 3d Ed., W.H. Freeman and Company, N.Y. 1988, inside back cover);

(v) Fields 5-7 are the x-axis, y-axis and z-axis positions of the atom;

(vi) Field 8 (often a "1.00") designates occupancy at that position;

(vii) Field 9 designates the B-factor;

(viii) Field 10 designates the molecule designation. Three molecules (designated a, b, and c) of G-CSF crystallized together as a unit. The designation a, b, or c indicates which coordinates are from which molecule. The number after the letter (1, 2, or 3) indicates the assigned amino acid residue position, with molecule A having assigned positions 10-175, molecule B having assigned positions 210-375, and molecule C having assigned positions 410-575. These positions were so designated so that there would be no overlap among the three molecules which crystallized together. (The "W" designation indicates water).

FIGURE 6 is a schematic representation of the strategy involved in refining the crystallization matrix for parameters involved in crystallization. The crystallization matrix corresponds to the final concentration of the components (salts, buffers and precipitants) of the crystallization solutions in the wells of a 24 well tissue culture plate. These concentrations are produced by pipetting the appropriate volume of stock solutions into the wells of the microtiter plate. To design the matrix, the crystallographer decides on an upper and lower concentration of the component. These upper and lower concentrations can be pipetted along either the rows (e.g., A1-A6, B1-B6, C1-C6 or D1-D6) or along the entire tray (A1-D6). The former method is useful for checking reproducibility of crystal growth of a single component along a limited number of wells, whereas the later method is more useful in initial screening. The results of several stages of refinement of the crystallization matrix are illustrated by a representation of three plates. The increase in shading in the wells indicates a positive crystallization result which, in the final stages, would be X-ray quality crystals but in the initial stages could be oil droplets, granular precipitates or small crystals approximately less than 0.05 mm in size. Part A represents an initial screen of one parameter in which the range of concentration between the first well (A1) and last well (D6) is large and the concentration increase between wells is calculated as (-(concentration A1)-(concentration D6))/23). Part B represents that in later stages of the crystallization matrix refinement of the concentration spread between A1 and D6 would be reduced which would result in more crystals formed per plate. Part C indicates a final stage of matrix refinement in which quality crystals are found in most wells of the plate.

Detailed Description of the Invention

The present invention grows out of the discovery of the three dimensional structure of G-CSF. This three dimensional structure has been expressed via computer program for stereoscopic viewing. By viewing this stereoscopically, structure-function relationships identified and G-CSF analogs have been designed and made.

The Overall Three Dimensional Structure of G-CSF

The G-CSF used to ascertain the structure was a non-glycosylated 174 amino acid species having an extra N-terminal methionine residue incident to bacterial expression. The DNA and amino acid sequence of this G-CSF are illustrated in FIGURE 1.

Overall, the three dimensional structure of G-CSF is predominantly helical, with 103 of the 175 residues forming a 4-alpha-helical bundle. The only other secondary structure is found in the loop between the first two long helices where a 4 residue 3^{10} helix is immediately followed by a 6 residue alpha helix. As shown in FIGURE 2, the overall structure has been compared with the structure reported for other proteins: growth hormone (Abdel-Meguid et al., PNAS-USA 84: 6434 (1987) and Vos et al., Science 255: 305-312 (1992)), granulocyte macrophage colony stimulating factor (Diederichs et al., Science 254: 1779-1782 (1991), interferon-β (Senda et al., EMBO J. 11: 3193-3201 (1992)), interleukin-2 (McKay Science 257: 1673-1677 (1992)) and interleukin-4 (Powers et al., Science 256: 1673-1677 (1992), and Smith et al., J. Mol. Biol. 224: 899-904 (1992)). Structural similarity among these growth factors occurs despite the absence of similarity in their amino acid sequences.

Presently, the structural information was correlation of G-CSF biochemistry, and this can be summarized as follows (with sequence position 1 being at the N-terminus):

Sequence Position	Description of Structure	Analysis
1-10	Extended chain	Deletion causes no loss of biological activity
Cys 18	Partially buried	Reactive with DTNB and Thimersososl but not with iodo-acetate
34	Alternative splice site	Insertion reduces biological activity
20-47 (inclusive)	Helix A, first disulfide and portion of AB helix	Predicted receptor binding region based on neutralizing antibody data
20, 23, 24	Helix A	Single alanine mutation of residue(s) reduces biological activity. Predicted receptor binding (Site B).
165-175 (inclusive)	Carboxy terminus	Deletion reduces biological activity

This biochemical information, having been gleaned from antibody binding studies, see Layton et al., Biochemistry 266: 23815-23823 (1991), was superimposed on the three-dimensional structure in order to design G-CSF analogs. The design, preparation, and testing of these G-CSF analogs is described in Example 1 below.

EXAMPLE 1

This Example describes the preparation of crystalline G-CSF, the visualization of the three dimensional structure of recombinant human G-CSF via computer-generated image, the preparation of analogs, using site-directed mutagenesis or nucleic acid amplification methods, the biological assays and HPLC analysis used to analyze the G-CSF analogs, and the resulting determination of overall structure/function relationships. All cited publications are herein incorporated by reference.

A. Use of Automated Crystallization

The need for a three-dimensional structure of recombinant human granulocyte colony stimulating factor (r-hu-G-CSF), and the availability of large quantities of the purified protein, led to methods of crystal growth by incomplete factorial sampling and seeding. Starting with the implementation of incomplete factorial

crystallization described by Jancarik and Kim· J. Appl. Crystallogr. 24: 409 (1991) solution conditions that yielded oil droplets and birefringence aggregates were ascertained. Also, software and hardware of an automated pipetting system were modified to produce some 400 different crystallization conditions per day. Weber, J. Appl. Crystallogr. 20: 366-373 (1987). This procedure led to a crystallization solution which produced r-hu-G-CSF crystals.

The size, reproducibility and quality of the crystals was improved by a seeding method in which the number of "nucleation initiating units" was estimated by serial dilution of a seeding solution. These methods yielded reproducible growth of 2.0 mm r-hu-G-CSF crystals. The space group of these crystals is $P2_12_12_1$ with cell dimensions of a = 90 Å, b = 110 Å and c = 49 Å, and they diffract to a resolution of 2.0 Å.

1. Overall Methodology

To search for the crystallizing conditions of a new protein, Carter and Carter, J. Biol. Chem. 254: 122219-12223 (1979) proposed the incomplete factorial method. They suggested that a sampling of a large number of randomly selected, but generally probable, crystallizing conditions may lead to a successful combination of reagents that produce protein crystallization. This idea was implemented by Jancarik and Kim, J. Appl. Crystallogr. 24: 409(1991), who described 32 solutions for the initial crystallization trials which cover a range of pH, salts and precipitants. Here we describe an extension of their implementation to an expanded set of 70 solutions. To minimize the human effort and error of solution preparation, the method has been programmed for an automatic pipetting machine.

Following Weber's method of successive automated grid searching (SAGS), J.Cryst. Growth 90: 318-324(1988), the robotic system was used to generate a series of solutions which continually refined the crystallization conditions of temperature, pH, salts and precipitant. Once a solution that could reproducibly grow crystals was determined, a seeding technique which greatly improved the quality of the crystals was developed. When these methods were combined, hundreds of diffraction quality crystals (crystals diffracting to at least about 2.5 Angstroms, preferably having at least portions diffracting to below 2 Angstroms, and more preferably, approximately 1 Angstrom) were produced in a few days.

Generally, the method for crystallization, which may be used with any protein one desires to crystallize, comprises the steps of:

(a) combining aqueous aliquots of the desired protein with either (i) aliquots of a salt solution, each aliquot having a different concentration of salt; or (ii) aliquots of a precipitant solution, each aliquot having a different concentration of precipitant, optionally wherein each combined aliquot is combined in the presence of a range of pH;

(b) observing said combined aliquots for precrystalline formations, and selecting said salt or precipitant combination and said pH which is efficacious in producing precrystalline forms, or, if no precrystalline forms are so produced, increasing the protein starting concentration of said aqueous aliquots of protein;

(c) after said salt or said precipitant concentration is selected, repeating step (a) with said previously unselected solution in the presence of said selected concentration; and

(d) repeating step (b) and step (a) until a crystal of desired quality is obtained.

The above method may optionally be automated, which provides vast savings in time and labor. Preferred protein starting concentrations are between 10mg/ml and 20mg/ml, however this starting concentration will vary with the protein (the G-CSF below was analyzed using 33mg/ml). A preferred range of salt solution to begin analysis with is (NaCl) of 0-2.5M. A preferred precipitant is polyethylene glycol 8000, however, other precipitants include organic solvents (such as ethanol), polyethylene glycol molecules having a molecular weight in the range of 500-20,000, and other precipitants known to those skilled in the art. The preferred pH range is pH 4.5 , 5.0, 5.5, 6.0, 6.5, 7.0, 7.5, 8.0, 8.5, and 9.0. Precrystallization forms include oils, birefringement precipitants, small crystals (< approximately 0.05 mm), medium crystals (approximately 0.5 to .5 mm) and large crystals (> approximately 0.5 mm). The preferred time for waiting to see a crystalline structure is 48 hours, although weekly observation is also preferred, and generally, after about one month, a different protein concentration is utilized (generally the protein concentration is increased). Automation is preferred, using the Accuflex system as modified. The preferred automation parameters are described below.

Generally, protein with a concentration between 10 mg/ml and 20 mg/ml was combined with a range of NaCl solutions from 0-2.5 M, and each such combination was performed (separately) in the presence of the above range of concentrations. Once a precrystallization structure is observed, that salt concentration and pH range are optimized in a separate experiment, until the desired crystal quality is achieved. Next, the precipitant concentration, in the presence of varying levels of pH is also optimized. When both are optimized, the optimal conditions are performed at once to achieve the desired result (this is diagrammed in

FIGURE 6).

a. Implementation of an automated pipetting system

Drops and reservoir solutions were prepared by an Accuflex pipetting system (ICN Pharmaceuticals, Costa Mesa, CA) which is controlled by a personal computer that sends ASCII codes through a standard serial interface. The pipetter samples six different solutions by means of a rotating valve and pipettes these solutions onto a plate whose translation in a x-y coordinate system can be controlled. The vertical component of the system manipulates a syringe that is capable both of dispensing and retrieving liquid.

The software provided with the Accuflex was based on the SAGS method as proposed by Cox and Weber, J.Appl. Crystallogr. 20: 366-373 (1987). This method involves the systematic variation of two major crystallization parameters, pH and precipitant concentration, with provision to vary two others. While building on these concepts, the software used here provided greater flexibility in the design and implementation of the crystallization solutions used in the automated grid searching strategy. As a result of this flexibility the present software also created a larger number of different solutions. This is essential for the implementation of the incomplete factorial method as described in that section below.

To improve the speed and design of the automated grid searching strategy, the Accuflex pipetting system required software and hardware modifications. The hardware changes allowed the use of two different micro-titer trays, one used for handing drop and one used for sitting drop experiments, and a Plexiglas tray which held 24 additional buffer, salt and precipitant solutions. These additional solutions expanded the grid of crystallizing conditions that could be surveyed.

To utilize the hardware modifications, the pipetting software was written in two subroutines; one subroutine allows the crystallographer to design a matrix of crystallization solutions based on the concentrations of their components and the second subroutine to translate these concentrations into the computer code which pipettes the proper volumes of the solutions into the crystallization trays. The concentration matrices can be generated by either of two programs. The first program (MRF, available from Amgen, Inc., Thousand Oaks, CA) refers to a list of stock solution concentrations supplied by the crystallographer and calculates the required volume to be pipette to achieve the designated concentration. The second method, which is preferred, incorporates a spread sheet program (Lotus) which can be used to make more sophisticated gradients of precipitants or pH. The concentration matrix created by either program is interpreted by the control program (SUX, a modification of the program found in the Accuflex pipetter originally and available from Amgen, Inc., Thousand Oaks, CA) and the wells are filled accordingly.

b. Implementation of the Incomplete Factorial Method

The convenience of the modified pipetting system for preparing diverse solutions improved the implementation of an expanded incomplete factorial method. The development of a new set of crystallization solutions having "random" components was generated using the program INFAC, Carter et al., J.Cryst. Growth 90: 60-73(1988) which produced a list containing 96 random combinations of one factor from three variables. Combinations of calcium and phosphate which immediately precipitated were eliminated, leaving 70 distinct combinations of precipitants, salts and buffers. These combinations were prepared using the automated pipetter and incubated for 1 week. The mixtures were inspected and solutions which formed precipitants were prepared again with lower concentrations of their components. This was repeated until all wells were clear of precipitant.

c. Crystallization of r-hu-G-CSF

Several different crystallization strategies were used to find a solution which produced x-ray quality crystals. These strategies included the use of the incomplete factorial method, refinement of the crystallization conditions using successive automated grid searches (SAGS), implementation of a seeding technique and development of a crystal production procedure which yielded hundreds of quality crystals overnight. Unless otherwise noted the screening and production of r-hu-G-CSF crystals utilized the hanging drop vapor diffusion method. Afinsen et al., Physical principles of protein crystallization. In: Eisenberg (ed.), Advances in Protein Chemistry 41: 1-33 (1991).

The initial screening for crystallization conditions of r-hu-G-CSF used the Jancarik and Kim, J.Appl.Crystallogr. 24: 409(1991) incomplete factorial method which resulted in several solutions that produced "precrystallization" results. These results included birefringent precipitants, oils and very small crystals (< .05 mm). These precrystallizations solutions then served as the starting points for systematic

screening.

The screening process required the development of crystallization matrices. These matrices corresponded to the concentration of the components in the crystallization solutions and were created using the IBM-PC based spread sheet Lotus™ and implemented with the modified Accuflex pipetting system. The strategy in designing the matrices was to vary one crystallization condition (such as salt concentration) while holding the other conditions such as pH, and precipitant concentration constant. At the start of screening, the concentration range of the varied condition was large but the concentration was successively refined until all wells in the micro-titer tray produced the same crystallization result. These results were scored as follows: crystals, birefringement precipitate, granular precipitate, oil droplets and amorphous mass. If the concentration of a crystallization parameter did not produce at least a precipitant, the concentration of that parameter was increased until a precipitant formed. After each tray was produced, it was left undisturbed for at least two days and then inspected for crystal growth. After this initial screening, the trays were then inspected on a weekly basis.

From this screening process, two independent solutions with the same pH and precipitant but differing in salts (MgCl, $LiSO_4$) were identified which produced small (0.1 x 0.05 x 0.05 mm) crystals. Based on these results, a new series of concentration matrices were produced which varied MgCl with respect to $LiSO_4$ while keeping the other crystallization parameters constant. This series of experiments resulted in identification of a solution which produced diffraction quality crystals (> approximately 0.5 mm) in about three weeks. To find this crystallization growth solution (100 mM Mes pH 5.8, 380 mM $MgCl_2$, 220 mM LiSO4 and 8% PEG 8k) approximately 8,000 conditions had been screened which consumed about 300 mg of protein.

The size of the crystals depended on the number of crystals forming per drop. Typically 3 to 5 crystals would be formed with average size of (1.0 x 0.7 x 0.7 mm). Two morphologies which had an identical space group ($P2_12_12_1$) and unit cell dimensions a = 90.2, b = 110.2, c = 49.5 were obtained depending on whether or not seeding (see below) was implemented. Without seeding, the r-hu-G-CSF crystals had one long flat surface and rounded edges.

When seeding was employed, crystals with sharp faces were observed in the drop within 4 to 6 hours (0.05 by 0.05 by 0.05 mm). Within 24 hours, crystals had grown to (0.7 by 0.7 by 0.7 mm) and continued to grow beyond 2 mm depending on the number of crystals forming in the drop.

d. Seeding and determination of nucleation initiation sites.

The presently provided method for seeding crystals establishes the number of nucleation initiation units in each individual well used (here, after the optimum conditions for growing crystals had been determined). The method here is advantageous in that the number of "seeds" affects the quality of the crystals, and this in turn affects the degree of resolution. The present seeding here also provides advantages in that with seeding, G-CSF crystal grows in a period of about 3 days, whereas without seeding, the growth takes approximately three weeks.

In one series of production growth (see methods), showers of small but well defined crystals were produced overnight (<0.01 x 0.01 x0.01 mm). Crystallization conditions were followed as described above except that a pipette tip employed in previously had been reused. Presumably, the crystal showering effect was caused by small nucleation units which had formed in the used tip and which provided sites of nucleation for the crystals. Addition of a small amount (0.5 ul) of the drops containing the crystal showers to a new drop under standard production growth conditions resulted in a shower of crystals overnight. This method was used to produce several trays of drops containing crystal showers which we termed "seed stock".

The number of nucleation initiation units (NIU) contained within the "seed stock" drops was estimated to attempt to improve the reproducibility and quality of the r-hu-GCSF crystals. To determine the number of NIU in the "seed stock", an aliquot of the drop was serially diluted along a 96 well microtiter plate. The microtiter plate was prepared by adding 50 ul of a solution containing equal volumes of r-hu-G-CSF (33 mg/ml) and the crystal growth solution (described above) in each well. An aliquot (3 ul) of one of the "seed stock" drops was transferred to the first well of the microtiter plate. The solution in the well was mixed and 3 ul was then transferred to the next well along the row of the microtiter plate. Each row of the microtiter plate was similarly prepared and the tray was sealed with plastic tape. Overnight, small crystals formed in the bottom of the wells of the microtiter plate and the number of crystals in the wells were correlated to the dilution of the original "seed stock". To produce large single crystals, the "seed stock" drop was appropriately diluted into fresh CGS and then an aliquot of this solution containing the NIU was transferred to a drop

Once crystallization conditions had been optimized, crystals were grown in a production method in which 3 ml each of CGS and r-hu-G-CSF (33 mg/ml) were mixed to create 5 trays (each having 24 wells). This method included the production of the refined crystallization solution in liter quantities, mixing this solution with protein and placing the protein/crystallization solution in either hanging drop or sitting drop trays. This process typically yielded 100 to 300 quality crystals (>0.5 mm) in about 5 days.

e. Experimental Methods

Materials

Crystallographic information was obtained starting with r-hu-met-G-CSF with the amino acid sequence as provided in FIGURE 1 with a specific activity of 1.0 +/- 0.6 x 10^8 U/mg (as measured by cell mitogenesis assay in a 10 mM acetate buffer at pH 4.0 (in Water for Injection) at a concentration of approximately 3 mg/ml solution was concentrated with an Amicon concentrator at 75 psi using a YM10 filter. The solution was typically concentrated 10 fold at 4 °C and stored for several months.

Initial Screening

Crystals suitable for X-ray analysis were obtained by vapor-diffusion equilibrium using hanging drops. For preliminary screening, 7 ul of the protein solution at 33 mg/ml (as prepared above) was mixed with an equal volume of the well solution, placed on siliconized glass plates and suspended over the well solution utilizing Linbro tissue culture plates (Flow Laboratories, McLean, Va). All of the pipetting was performed with the Accuflex pipetter, however, trays were removed from the automated pipetter after the well solutions had been created and thoroughly mixed for at least 10 minutes with a table top shaker. The Linbro trays were then returned to the pipetter which added the well and protein solutions to the siliconized cover slips. The cover slips were then inverted and sealed over 1 ml of the well solutions with silicon grease.

The components of the automated crystallization system are as follows. A PC-DOS computer system was used to design a matrix of crystallization solutions based on the concentration of their components. These matrices were produced with either MRF of the Lotus spread sheet (described above). The final product of these programs is a data file. This file contains the information required by the SUX program to pipette the appropriate volume of the stock solutions to obtain the concentrations described in the matrices. The SUX program information was passed through a serial I/O port and used to dictate to the Accuflex pipetting system the position of the valve relative to the stock solutions, the amount of solution to be retrieved, and then pipetted into the wells of the microtiter plates and the X-Y position of each well (the column/row of each well). Addition information was transmitted to the pipetter which included the Z position (height) of the syringe during filling as well as the position of a drain where the system pauses to purge the syringe between fillings of different solutions. The 24 well microtiter plate (either Linbro or Cryschem) and cover slip holder was placed on a plate which was moved in the X-Y plane. Movement of the plate allowed the pipetter to position the syringe to pipette into the wells. It also positioned the coverslips and vials and extract solutions from these sources. Prior the pipetting, the Linbro microtiter plates had a thin film of grease applied around the edges of the wells. After the crystallization solutions were prepared in the wells and before they were transferred to the cover slips, the microtiter plate was removed from the pipetting system, and solutions were allowed to mix on a table top shaker for ten minutes. After mixing, the well solution was either transferred to the cover slips (in the case of the hanging drop protocol) or transferred to the middle post in the well (in the case of the sitting drop protocol). Protein was extracted from a vial and added to the coverslip drop containing the well solution (or to the post). Plastic tape was applied to the top of the Cryschem plate to seal the wells.

Production Growth

Once conditions for crystallization had been optimized, crystal growth was performed utilizing a "production" method. The crystallization solution which contained 100 mM Mes pH 5.8, 380 mM MgCl2, 220 mM LiSO4, and 8% PEG 8K was made in 1 liter quantities. Utilizing an Eppindorf syringe pipetter, 1 ml aliquots of this solution were pipetted into each of the wells of the Linbro plate. A solution containing 50% of this solution and 50% G-CSF (33 mg/ml) was mixed and pipetted onto the siliconized cover slips. Typical volumes of these drops were between 50 and 100 ul and because of the large size of these drops, great care was taken in flipping the coverslips and suspending the drops over the wells.

Data Collection

The structure has been refined with X-PLOR (Bruniger, X-PLOR version 3.0, A system for crystallography and NMR, Yale University, New Haven CT) against 2.2Å data collected on an R-AXIS (Molecular Structure, Corp. Houston, TX) imaging plate detector.

f. Observations

As an effective recombinant human therapeutic, r-hu-G-CSF has been produced in large quantities and gram levels have been made available for structural analysis. The crystallization methods provided herein are likely to find other applications as other proteins of interest become available. This method can be applied to any crystallographic project which has large quantities of protein (approximately >200 mg). As one skilled in the art will recognize, the present materials and methods may be modified and equivalent materials and methods may be available for crystallization of other proteins.

B. Computer Program For Visualizing The Three Dimensional Structure of G-CSF

Although diagrams, such as those in the Figures herein, are useful for visualizing the three dimensional structure of G-CSF, a computer program which allows for stereoscopic viewing of the molecule is contemplated as preferred. This stereoscopic viewing, or "virtual reality" as those in the art sometimes refer to it, allows one to visualize the structure in its three dimensional form from every angle in a wide range of resolution, from macromolecular structure down to the atomic level. The computer programs contemplated herein also allow one to change perspective of the viewing angle of the molecule, for example by rotating the molecule. The contemplated programs also respond to changes so that one may, for example, delete, add, or substitute one or more images of atoms, including entire amino acid residues, or add chemical moieties to existing or substituted groups, and visualize the change in structure.

Other computer based systems may be used; the elements being: (a) a means for entering information, such as orthogonal coordinates or other numerically assigned coordinates of the three dimensional structure of G-CSF; (b) a means for expressing such coordinates, such as visual means so that one may view the three dimensional structure and correlate such three dimensional structure with the composition of the G-CSF molecule, such as the amino acid composition; (c) optionally, means for entering information which alters the composition of the G-CSF molecule expressed, so that the image of such three dimensional structure displays the altered composition.

The coordinates for the preferred computer program used are presented in FIGURE 5. The preferred computer program is Insight II, version 4, available from Biosym in San Diego, CA. For the raw crystallographic structure, the observed intensities of the diffraction data ("F-obs") and the orthogonal coordinates are also deposited in the Protein Data Bank, Chemistry Department, Brookhaven National Laboratory, Upton, New York 119723, USA and these are herein incorporated by reference.

Once the coordinates are entered into the Insight II program, one can easily display the three dimensional G-CSF molecule representation on a computer screen. The preferred computer system for display is Silicon Graphics 320 VGX (San Diego, CA). For stereoscopic viewing, one may wear eyewear (Crystal Eyes, Silicon Graphics) which allows one to visualize the G-CSF molecule in three dimensions stereoscopically, so one may turn the molecule and envision molecular design.

Thus, the present invention provides a method of designing or preparing a G-CSF analog with the aid of a computer comprising:

(a) providing said computer with the means for displaying the three dimensional structure of a G-CSF molecule including displaying the composition of moieties of said G-CSF molecule, preferably displaying the three dimensional location of each amino acid, and more preferably displaying the three dimensional location of each atom of a G-CSF molecule;

(b) viewing said display;

(c) selecting a site on said display for alteration in the composition of said molecule or the location of a moiety; and

(d) preparing a G-CSF analog with such alteration.

The alteration may be selected based on the desired structural characteristics of the end-product G-CSF analog, and considerations for such design are described in more detail below. Such considerations include the location and compositions of hydrophobic amino acid residues, particularly residues internal to the helical structures of a G-CSF molecule which residues, when altered, alter the overall structure of the internal core of the molecule and may prevent receptor binding; the location and compositions of external

loop structures, alteration of which may not affect the overall structure of the G-CSF molecule.

FIGURES 2-4 illustrate the overall three dimensional conformation in different ways. The topological diagram, the ribbon diagram, and the barrel diagram all illustrate aspects of the conformation of G-CSF.

FIGURE 2 illustrates a comparison between G-CSF and other molecules. There is a similarity of architecture, although these growth factors differ in the local conformations of their loops and bundle geometrics. The up-up-down-down topology with two long crossover connections is conserved, however, among all six of these molecules, despite the dissimilarity in amino acid sequence.

FIGURE 3 illustrates in more detail the secondary structure of recombinant human G-CSF. This ribbon diagram illustrates the handedness of the helices and their positions relative to each other.

FIGURE 4 illustrates in a different way the conformation of recombinant human G-CSF. This "barrel" diagram illustrates the overall architecture of recombinant human G-CSF.

C. Preparation of Analogs Using M13 Mutagenesis

This example relates to the preparation of G-CSF analogs using site directed mutagenesis techniques involving the single stranded bacteriophage M13, according to methods published in PCT Application No. WO 85/00817 (Souza et al., published February 28, 1985, herein incorporated by reference). This method essentially involves using a single-stranded nucleic acid template of the non-mutagenized sequence, and binding to it a smaller oligonucleotide containing the desired change in the sequence. Hybridization conditions allow for non-identical sequences to hybridize and the remaining sequence is filled in to be identical to the original template. What results is a double stranded molecule, with one of the two strands containing the desired change. This mutagenized single strand is separated, and used itself as a template for its complementary strand. This creates a double stranded molecule with the desired change.

The original G-CSF nucleic acid sequence used is presented in FIGURE 1, and the oligonucleotides containing the mutagenized nucleic acid(s) are presented in Table 2. Abbreviations used herein for amino acid residues and nucleotides are conventional, see Stryer, Biochemistry, 3d Ed., W.H. Freeman and Company, N.Y., N.Y. 1988, inside back cover.

The original G-CSF nucleic acid sequence was first placed into vector M13mp21. The DNA from single stranded phage M13mp21 containing the original G-CSF sequence was then isolated, and resuspended in water. For each reaction, 200 ng of this DNA was mixed with a 1.5 pmole of phosphorylated oligonucleotide (Table 2) and suspended in 0.1M Tris, 0.01M $MgCl_2$, 0.005M DTT, 0.1mM ATP, pH 8.0. The DNAs were annealed by heating to 65 °C and slowly cooling to room temperature.

Once cooled, 0.5mM of each ATP, dATP, dCTP, dGTP, TTP, 1 unit of T4 DNA ligase and 1 unit of Klenow fragment of E. coli polymerase 1 were added to the 1 unit of annealed DNA in 0.1M Tris, 0.025M NaCl, 0.01M $MgCl_2$, 0.01M DTT, pH 7.5.

The now double stranded, closed circular DNA was used to transfect E. coli without further purification. Plaques were screened by lifting the plaques with nitrocellulose filters, and then hybridizing the filters with single stranded DNA end-labeled with P^{32} for 1 hour at 55-60 °C. After hybridization, the filters were washed at 0-3 °C below the melt temperature of the oligo (2 °C for A-T, 4 °C for G-C) which selectively left autoradiography signals corresponding to plaques with phage containing the mutated sequence. Positive clones were confirmed by sequencing.

Set forth below are the oligonucleotides used for each G-CSF analog prepared via the M13 mutagenesis method. The nomenclature indicates the residue and the position of the original amino acid (e.g., Lysine at position 17), and the residue and position of the substituted amino acid (e.g., arginine 17). A substitution involving more than one residue is indicated via superscript notation, with commas between the noted positions or a semicolon indicating different residues. Deletions with no substitutions are so noted. The oligonucleotide sequences used for M13-based mutagenesis are next indicated; these oligonucleotides were manufactured synthetically, although the method of preparation is not critical, any nucleic acid synthesis method and/or equipment may be used. The length of the oligo is also indicated. As indicated above, these oligos were allowed to contact the single stranded phage vector, and then single nucleotides were added to complete the G-CSF analog nucleic acid sequence.

Table 2

G-CSF ANALOGS	SEQUENCES(5'-> 3')	Length(nucleotide)	Seq. ID
Lys^{17}->Arg^{17}	CTT TCT GCT GCG TTG TCT GGA ACA	24	3
Lys^{24}->Arg^{24}	ACA GGT TCG TCG TAT CCA GGG TG	23	4
Lys^{35}->Arg^{35}	CAC TGC AAG AAC GTC TGT GCG CT	23	5
Lys^{41}->Arg^{41}	CGC TAC TTA CCG TCT GTG CCA TC	23	6
$Lys^{17,24,35}$-> $Arg^{17,24,35}$	CTT TCT GCT GCG TTG TCT GGA ACA	24	7
	ACA GGT TCG TCG TAT CCA GGG TG	23	8
	CAC TGC AAG AAC GTC TGT GCG CT	23	9
$Lys^{17,24,41}$-> $Arg^{17,24,41}$	CTT TCT GCT GCG TTG TCT GGA ACA	24	10
	ACA GGT TCG TCG TAT CCA GGG TG	23	11
	CGC TAC TTA CCG TCT GTC CCA TC	23	12
$Lys^{17,35,41}$-> $Arg^{17,35,41}$	CTT TCT GCT GCG TTG TCT GGA ACA	24	13
	CAC TGC AAG AAC GTC TGT GCG CT	23	14
	CGC TAC TTA CCG TCT GTG CCA TC	23	15
$Lys^{24,35,41}$-> $Arg^{24,35,41}$	ACA GGT TCG TCG TAT CCA GGG TG	23	16
	CAC TGC AAG AAC GTC TGT GCG CT	23	17
	CGC TAC TTA CCG TCT GTG CCA TC	23	18

Table 2 (con't)

G-CSF ANALOGS	SEQUENCES (5'-> 3')	Length (nucleotide)	Seq. ID
$Lys^{17,24,35,41}$-> $Arg^{17,24,35,41}$	CTT TCT GCT GCG TTG TCT GGA ACA	24	19
	ACA GGT TCG TCG TAT CCA GGG TG	23	20
	CAC TGC AAG AAC GTC TGT GCG CT	23	21
	CGC TAC TTA CCG TCT GTG CCA TC	23	22
Cys^{18}->Ala^{18}	TCT GCT GAA AGC TCT GGA ACA GG	23	23
Gln^{68}->Glu^{68}	CTT GTC CAT CTG AAG CTC TTC AG	23	24
$Cys^{37,43}$-> $Ser^{37,43}$	GAA AAA CTG TCC GCT ACT TAC AAA CTG TCC CAT CCG G	37	25
Gln^{26}->Ala^{26}	TTC GTA AAA TCG CGG GTG ACG G	22	26
Gln^{174}->Ala^{174}	TCA TCT GGC TGC GCC GTA ATA G	22	27
Arg^{170}->Ala^{170}	CCG TGT TCT GGC TCA TCT GGC T	22	28
Arg^{167}->Ala^{167}	GAA GTA TCT TAC GCT GTT CTG CGT	24	29
Deletion 167	GAA GTA TCT TAC TAA GTT CTG CGT C	25	30
Lys^{41}->Ala^{41}	CGC TAC TTA CGC ACT GTG CCA T	22	31
His^{44}->Lys^{44}	CAA ACT GTG CAA GCC GGA AGA G	22	32
Glu^{47}->Ala^{47}	CAT CCG GAA GCA CTG GTA CTG C	22	33

Table 2 (con't)

G-CSF ANALOGS	SEQUENCES(5'-> 3')	Length(nucleotide)	Seq. ID
Arg^{23}->Ala^{23}	GGA ACA GGT TGC TAA AAT CCA GG	23	34
Lys^{24}->Ala^{24}	GAA CAG GTT CGT GCG ATC CAG GGT G	25	35
Glu^{20}->Ala^{20}	GAA ATG TCT GGC ACA GGT TCG T	22	36
Asp^{28}->Ala^{28}	TCC AGG GTG CCG GTG CTG C	19	37
Met^{127}->Glu^{127}	AAG AGC TCG GTG AGG CAC CAG CT	23	38
Met^{138}->Glu^{138}	CTC AAG GTG CTG AGC CGG CAT TC	23	39
Met^{127}->Leu^{127}	GAG CTC GGT CTG GCA CCA GC	20	40
Met^{138}->Leu^{138}	TCA AGG TGC TCT GCC GGC ATT	21	41
Ser^{13}->Ala^{13}	TCT GCC GCA AGC CTT TCT GCT GA	23	42
Lys^{17}->Ala^{17}	CTT TCT GCT GGC ATG TCT GGA ACA	24	43
Gln^{121}->Ala^{121}	CTA TTT GGC AAG CGA TGG AAG AGC	24	44
Glu^{124}->Ala^{124}	CAG ATG GAA GCG CTC GGT ATG	21	45

Table 2 (con't)

G-CSF ANALOGS	SEQUENCES (5'-> 3')	Length(nucleotide)	Seq. ID
$Met^{127,138}$-> $Leu^{127,138}$	GAG CTC GGT CTG GCA CCA GC	20	46
	TCA AGG TGC TCT GCC GGC ATT	21	47
**Glu^{20}->Ala^{20}; Ser^{13}->Gly^{13}	GAA ATG TCT GGC ACA GGT TCG T	22	48

** This analog came about during the preparation of G-CSF analog Glu^{20}->Ala^{20}. As several clones were being sequenced to identify the Glu^{20}->Ala^{20} analog, the Glu^{20}->Ala^{20}; Ser^{13}->Gly^{13} analog was identified. This double mutant was the result of an in vitro Klenow DNA polymerase reaction mistake.

D. Preparation of G-CSF Analogs Using DNA Amplification

This example relates to methods for producing G-CSF analogs using a DNA amplification technique. Essentially, DNA encoding each analog was amplified in two separate pieces, combined, and then the total

sequence itself amplified. Depending upon where the desired change in the original G-CSF DNA was to be made, internal primers were used to incorporate the change, and generate the two separate amplified pieces. For example, for amplification of the 5' end of the desired analog DNA, a 5' flanking primer (complementary to a sequence of the plasmid upstream from the G-CSF original DNA) was used at one end of the region to be amplified, and an internal primer, capable of hybridizing to the original DNA but incorporating the desired change, was used for priming the other end. The resulting amplified region stretched from the 5' flanking primer through the internal primer. The same was done for the 3' terminus, using a 3' flanking primer (complementary to a sequence of the plasmid downstream from the G-CSF original DNA) and an internal primer complementary to the region of the intended mutation. Once the two "halves" (which may or may not be equal in size, depending on the location of the internal primer) were amplified; the two "halves" were allowed to connect. Once connected, the 5' flanking primer and the 3' flanking primer were used to amplify the entire sequence containing the desired change.

If more than one change is desired, the above process may be modified to incorporate the change into the internal primer, or the process may be repeated using a different internal primer. Alternatively, the gene amplification process may be used with other methods for creating changes in nucleic acid sequence, such as the phage based mutagenesis technique as described above. Examples of process for preparing analogs with more than one change are described below.

To create the G-CSF analogs described below, the template DNA used was the sequence as in FIGURE 1 plus certain flanking regions (from a plasmid containing the G-CSF coding region). These flanking regions were used as the 5' and 3' flanking primers and are set forth below. The amplification reactions were performed in 40 ul volumes containing 10 mM Tris-HCl, 1.5 mM $MgCl_2$, 50 mM KCl, 0.1 mg/ml gelatin, pH 8.3 at 20°C. The 40 ul reactions also contained 0.1mM of each dNTP, 10 pmoles of each primer, and 1 ng of template DNA. Each amplification was repeated for 15 cycles. Each cycle consisted of 0.5 minutes at 94°C, 0.5 minutes at 50°C, and 0.75 minutes at 72°C. Flanking primers were 20 nucleotides in length and internal primers were 20 to 25 nucleotides in length. This resulted in multiple copies of double stranded DNA encoding either the front portion or the back portion of the desired G-CSF analog.

For combining the two "halves," one fortieth of each of the two reactions was combined in a third DNA amplification reaction. The two portions were allowed to anneal at the internal primer location, as their ends bearing the mutation were complementary, and following a cycle of polymerization, give rise to a full length DNA sequence. Once so annealed, the whole analog was amplified using the 5' and 3' flanking primers. This amplification process was repeated for 15 cycles as described above.

The completed, amplified analog DNA sequence was cleaved with XbaI and XhoI restriction endonuclease to produce cohesive ends for insertion into a vector. The cleaved DNA was placed into a plasmid vector, and that vector was used to transform E. coli. Transformants were challenged with kanamycin at 50 ug/ml and incubated at 30°C. Production of G-CSF analog protein was confirmed by polyacrylamide gel electrophoresis of a whole cell lysate. The presence of the desired mutation was confirmed by DNA sequence analysis of plasmid purified from the production isolate. Cultures were then grown, and cells were harvested, and the G-CSF analogs were purified as set forth below.

Set forth below in Table 3 are the specific primers used for eachanalog made using gene amplification.

Table 3

Analog Seq. ID	Internal Primer(5'->3')	
His^{44}->Ala^{44}	5'primer-TTCCGGAGCGCACAGTTTG	49
	3'primer-CAAACTGTGGGCTCCGGAAGAGC	50
Thr^{117}->Ala^{117}	5'primer-ATGCCAAATTGCAGTAGCAAAG	51
	3'primer-CTTTGCTACTGCAATTTGGCAACA	52
Asp^{110}->Ala^{110}	5'primer-ATCAGCTACTGCTAGCTGCAGA	53
	3'primer-TCTGCAGCTAGCAGTAGCTGACT	54
Gln^{21}->Ala^{21}	5'primer-TTACGAACCGCTTCCAGACATT	55
	3'primer-AATGTCTGGAAGCGGTTCGTAAAAT	56
Asp^{113}->Ala^{113}	5'primer-GTAGCAAATGCAGCTACATCTA	57
	3'primer-TAGATGTAGCTGCATTTGCTACTAC	58
His^{53}->Ala^{53}	5'primer-CCAAGAGAAGCACCCAGCAG	59
	3'primer-CTGCTGGGTGCTTCTCTTGGGA	60
For each analog, the following 5' flanking primer was used:		
5'-CACTGGCGGTGATAATGAGC		61
For each analog, the following 3' flanking primer was used:		
3'-GGTCATTACGGACCGGATC		62

1. Construction of Double Mutation

To make G-CSF analog $Gln^{12,21}$->$Glu^{12,21}$, two separate DNA amplifications were conducted to create the two DNA mutations. The template DNA used was the sequence as in FIGURE 1 plus certain flanking regions (from a plasmid containing the G-CSF coding region). The precise sequences are listed below. Each of the two DNA amplification reactions were carried out using a Perkin Elmer/Cetus DNA Thermal Cycler. The 40 ul reaction mix consisted of 1X PCR Buffer (Cetus), 0.2 mM each of the 4 dXTPs (Cetus), 50 pmoles of each primer oligonucleotide, 2 ng of G-CSF template DNA (on a plasmid vector), and 1 unit of Taq polymerase (Cetus). The amplification process was carried out for 30 cycles. Each cycle consisted of 1minute at 94 • C, 2 minutes at 50 • C, and 3 minutes at 72 • C.

DNA amplification "A" used the oligonucleotides:
5' CCACTGGCGGTGATACTGAGC 3' (Seq. ID 63) and
5' AGCAGAAAGCTTTCCGGCAGAGAAGAAGCAGGA 3' (Seq. ID 64)

DNA amplification "B" used the oligonucleotides: 5' GCCGCAAAGCTTTCTGCTGAAATGTCTG-GAAGAGGTTCGTAAAATCCAGGGTGA 3' (Seq. ID 65) and
5' CTGGAATGCAGAAGCAAATGCCGGCATAGCACCTTCAGTCGGTTGCAGAGCTGGTGCCA 3' (Seq. ID 66)

From the 109 base pair double stranded DNA product obtained after DNA amplification "A", a 64 base pair XbaI to HindIII DNA fragment was cut and isolated that contained the DNA mutation Gln^{12}->Glu^{12}. From the 509 base pair double stranded DNA product obtained after DNA amplification "B", a 197 base pair HindIII to BsmI DNA fragment was cut and isolated that contained the DNA mutation Gln^{21}->Glu^{21}.

The "A" and "B" fragments were ligated together with a 4.8 kilo-base pair XbaI to BsmI DNA plasmid vector fragment. The ligation mix consisted of equal molar DNA restriction fragments, ligation buffer (25 mM Tris-HCl pH 7.8, 10 mM $MgCl_2$, 2 mM DTT, 0.5 mM rATP, and 100 ug/ml BSA) and T4 DNA ligase and was incubated overnight at 14 • C. The ligated DNA was then transformed into E. coli FM5 cells by electroporation using a Bio Rad Gene Pulsar apparatus (BioRad, Richmond, CA). A clone was isolated and the plasmid construct verified to contain the two mutations by DNA sequencing. This 'intermediate' vector also contained a deletion of a 193 base pair BsmI to BsmI DNA fragment. The final plasmid vector was constructed by ligation and transformation (as described above) of DNA fragments obtained by cutting and isolating a 2 kilo-base pair SstI to BamHI DNA fragment from the intermediate vector, a 2.8 kbp SstI to EcoRI DNA fragment from the plasmid vector, and a 360 bp BamHI to EcoRI DNA fragment from the

plasmid vector. The final construct was verified by DNA sequencing the G-CSF gene. Cultures were grown, and the cells were harvested, and the G-CSF analogs were purified as set forth below.

As indicated above, any combination of mutagenesis techniques may be used to generate a G-CSF analog nucleic acid (and expression product) having one or more than one alteration. The two examples above, using M13-based mutagenesis and gene amplification-based mutagenesis, are illustrative.

E. Expression of G-CSF Analog DNA

The G-CSF analog DNAs were then placed into a plasmid vector and used to transform E. coli strain FM5 (ATCC#53911). The present G-CSF analog DNAs contained on plasmids and in bacterial host cells are available from the American Type Culture Collection, Rockville, MD, and the accession designations are indicated below.

One liter cultures were grown in broth containing 10g tryptone, 5g yeast extract and 5g NaCl) at 30 • C until reaching a density at A^{600} of 0.5, at which point they were rapidly heated to 42 • C. The flasks were allowed to continue shaking at for three hours.

Other prokaryotic or eukaryotic host cells may also be used, such as other bacterial cells, strains or species, mammalian cells in culture (COS, CHO or other types) insect cells or multicellular organs or organisms, or plant cells or multicellular organs or organisms, and a skilled practitioner will recognize the appropriate host. The present G-CSF analogs and related compositions may also be prepared synthetically, as, for example, by solid phase peptide synthesis methds, or other chemical manufacturing techniques. Other cloning and expression systems will be apparent to those skilled in the art.

F. Purification of G-CSF Analog Protein

Cells were harvested by centrifugation (10,000 x G, 20 minutes, 4 • C). The pellet (usually 5 grams) was resuspended in 30 ml of 1mM DTT and passed three times through a French press cell at 10,000 psi. The broken cell suspension was centrifuged at 10,000g for 30 minutes, the supernatant removed, and the pellet resuspended in 30-40 ml water. This was recentrifuged at 10,000 x G for 30 minutes, and this pellet was dissolved in 25 ml of 2% Sarkosyl and 50mM Tris at pH 8. Copper sulfate was added to a concentration of 40uM, and the mixture was allowed to stir for at least 15 hours at 15-25 • C. The mixture was then centrifuged at 20,000 x G for 30 minutes. The resultant solubilized protein mixture was diluted four-fold with 13.3 mM Tris, pH 7.7, the Sarkosyl was removed, and the supernatant was then applied to a DEAE-cellulose (Whatman DE-52) column equilibrated in 20mM Tris, pH 7.7. After loading and washing the column with the same buffer, the analogs were eluted with 20mM Tris /NaCl (between 35mM to 100mM depending on the analog, as indicated below), pH 7.7. For most of the analogs, the eluent from the DEAE column was adjusted to a pH of 5.4, with 50% acetic acid and diluted as necessary (to obtain the proper conductivity) with 5mM sodium acetate pH 5.4. The solution was then loaded onto a CM-sepharose column equilibrated in 20 mM sodium acetate, pH 5.4. The column was then washed with 20mM NaAc, pH 5.4 until the absorbance at 280 nm was approximately zero. The G-CSF analog was then eluted with sodium acetate/NaCl in concentrations as described below in Table 4. The DEAE column eluents for those analogs not applied to the CM-sepharose column were dialyzed directly into 10mM NaAc, ph 4.0 buffer. The purified G-CSF analogs were then suitably isolated for in vitro analysis. The salt concentrations used for eluting the analogs varied, as noted above. Below, the salt concentrations for the DEAE cellulose column and for the CM-sepharose column are listed:

Table 4

Salt Concentrations

Analog	DEAE Cellulose	CM-Sepharose
Lys^{17}->Arg^{17}	35mM	37.5mM
Lys^{24}->Arg^{24}	35mM	37.5mM
Lys^{35}->Arg^{35}	35mM	37.5mM
Lys^{41}->Arg^{41}	35mM	37.5mM
$Lys^{17,24,35}$->$Arg^{17,24,35}$	35mM	37.5mM
$Lys^{17,35,41}$->$Arg^{17,35,41}$	35mM	37.5mM

Table 4 Con't

Analog	DEAE Cellulose	CM-Sepharose
$Lys^{24,35,41}$->$Arg^{24,35,41}$	35mM	37.5mM
$Lys^{17,24,35,41}$->$Arg^{17,24,35,41}$	35mM	37.5mM
$Lys^{17,24,41}$->$Arg^{17,24,41}$	35mM	37.5mM
Gln^{68}->Glu^{68}	60mM	37,5mM
$Cys^{37,43}$->$Ser^{37,43}$	40mM	37.5mM
Gln^{26}->Ala^{26}	40mM	40mM
Gln^{174}->Ala^{174}	40mM	40mM
Arg^{170}->Ala^{170}	40mM	40mM
Arg^{167}->Ala^{167}	40mM	40mM
Deletion 167*	N/A	N/A
Lys^{41}->Ala^{41}	160mM	40mM
His^{44}->Lys^{44}	40mM	60mM
Glu^{47}->Ala^{47}	40mM	40mM
Arg^{23}->Ala^{23}	40mM	40mM
Lys^{24}->Ala^{24}	120mM	40mM
Glu^{20}->Ala^{20}	40mM	60mM
Asp^{28}->Ala^{28}	40mM	80mM
Met^{127}->Glu^{127}	80mM	40mM
Met^{138}->Glu^{138}	80mM	40mM
Met^{127}->Leu^{127}	40mM	40mM
Met^{138}->Leu^{138}	40mM	40mM
Cys^{18}->Ala^{18}	40mM	37.5mM
$Gln^{12,21}$->$Glu^{12,21}$	60mM	37.5mM
$Gln^{12,21,68}$->$Glu^{12,21,68}$ Glu^{20}->Ala^{20}; Ser^{13}->Gly^{13}	60mM 40mM	37.5mM 80mM

Table 4 Con't

Analog	DEAE Cellulose	CM-Sepharose
$Met^{127,138}$->$Leu^{127,138}$	40mM	40mM
Ser^{13}->Ala^{13}	40mM	40mM
Lys^{17}->Ala^{17}	80mM	40mM
Gln^{121}->Ala^{121}	40mM	60mM
Gln^{21}->Ala^{21}	50mM	Gradient 0 -150mM
His^{44}->Ala^{44}**	40mM	N/A
His^{53}->Ala^{53}**	50mM	N/A
Asp^{110}->Ala^{110}**	40mM	N/A
Asp^{113}->Ala^{113}**	40mM	N/A
Thr^{117}->Ala^{117}**	50mM	N/A
Asp^{28}->Ala^{28}; Asp^{110} Ala^{110}**	50mM	N/A
Glu^{124}->Ala^{124}**	40mM	40mM

* For Deletion ^{167}, the data are unavailable.
** For these analogs, the DEAE cellulose column alone was use for purification.

The above purification methods are illustrative, and a skilled practitioner will recognize that other means are available for obtaining the present G-CSF analogs.

G. Biological Assays

Regardless of which methods were used to create the present G-CSF analogs, the analogs were subject to assays for biological activity. Tritiated thymidine assays were conducted to ascertain the degree of cell division. Other biological assays, however, may be used to ascertain the desired activity. Biological assays such as assaying for the ability to induce terminal differentiation in mouse WEHI-3B (D+) leukemic cell line, also provides indication of G-CSF activity. See Nicola, et al., Blood 54: 614-27 (1979). Other in vitro assays may be used to ascertain biological activity. See Nicola, Annu. Rev. Biochem. 58: 45-77 (1989). In general, the test for biological activity should provide analysis for the desired result, such as increase or decrease in biological activity (as compared to non-altered G-CSF), different biological activity (as compared to non-altered G-CSF), receptor affinity analysis, or serum half-life analysis. The list is incomplete, and those skilled in the art will recognize other assays useful for testing for the desired end result.

The ^{3}H-thymidine assay was performed using standard methods. Bone marrow was obtained from sacrificed female Balb C mice. Bone marrow cells were briefly suspended, centrifuged, and resuspended in a growth medium. A 160 ul aliquot containing approximately 10,000 cells was placed into each well of a 96 well micro-titer plate. Samples of the purified G-CSF analog(as prepared above) were added to each well, and incubated for 68 hours. Tritiated thymidine was added to the wells and allowed to incubate for 5 additional hours. After the 5 hour incubation time, the cells were harvested, filtered, and thoroughly rinsed. The filters were added to a vial containing scintillation fluid. The beta emissions were counted (LKB Betaplate scintillation counter). Standards and analogs were analyzed in triplicate, and samples which fell substantially above or below the standard curve were re-assayed with the proper dilution. The results

reported here are the average of the triplicate analog data relative to the unaltered recombinant human G-CSF standard results.

H. HPLC Analysis

High pressure liquid chromatography was performed on purified samples of analog. Although peak position on a reverse phase HPLC column is not a definitive indication of structural similarity between two proteins, analogs which have similar retention times may have the same type of hydrophobic interactions with the HPLC column as the non-altered molecule. This is one indication of an overall similar structure.

Samples of the analog and the non-altered recombinant human G-CSF were analyzed on a reverse phase (0.46 x 25 cm) Vydac 214TP54 column (Separations Group, Inc. Hesperia, CA). The purified analog G-CSF samples were prepared in 20 mM acetate and 40 mM NaCl solution buffered at pH 5.2 to a final concentration of 0.1 mg/ml to 5 mg/ml, depending on how the analog performed in the column. Varying amounts (depending on the concentration) were loaded onto the HPLC column, which had been equilibrated with an aqueous solution containing 1% isopropanol, 52.8% acetonitrile, and .38% trifluoro acetate (TFA). The samples were subjected to a gradient of 0.86%/minute acetonitrile, and .002% TFA.

I. Results

Presented below are the results of the above biological assays and HPLC analysis. Biological activity is the average of triplicate data and reported as a percentage of the control standard (non-altered G-CSF). Relative HPLC peak position is the position of the analog G-CSF relative to the control standard (non-altered G-CSF) peak. The "+" or "-" symbols indicate whether the analog HPLC peak was in advance of or followed the control standard peak (in minutes). Not all of the variants had been analyzed for relative HPLC peak, and only those so analyzed are included below. Also presented are the American Type Culture Collection designations for E. coli host cells containing the nucleic acids coding for the present analogs, as prepared above.

Table 5

Seq. ID	Variant	Analog	Relative HPLC Peak	ATCC No.	% Normal G-CSF Activity
67	1	Lys^{17}->Arg^{17}	N/A	69184	N/A
68	2	Lys^{24}->Arg^{24}	N/A	69185	N/A
69	3	Lys^{35}->Arg^{35}	N/A	69186	N/A
70	4	Lys^{41}->Arg^{41}	N/A	69187	N/A
71	5	$Lys^{17,24,35}$->$Arg^{17,24,35}$	N/A	69189	N/A
72	6	$Lys^{17,35,41}$->$Arg^{17,35,41}$	N/A	69192	N/A
73	7	$Lys^{24,35,41}$->$Arg^{24,35,41}$	N/A	69191	N/A
74	8	$Lys^{17,24,35,41}$ ->$Arg^{17,24,35,41}$	N/A	69193	N/A
75	9	$Lys^{17,24,41}$->$Arg^{17,24,41}$	N/A	69190	N/A
76	10	Gln^{68}->Glu^{68}	N/A	69196	N/A
77	11	$Cys^{37,43}$->$Ser^{37,43}$	N/A	69197	N/A
78	12	Gln^{26}->Ala^{26}	+.96	69201	51%
79	13	Gln^{174}->Ala^{174}	+.14	69202	100%
80	14	Arg^{170}->Ala^{170}	+.78	69203	100%

Table 5 Con't

Seq. ID	Variant	Analog	Relative HPLC Peak	ATCC No.	% Normal G-CSF Activity
81	15	Arg^{167}->Ala^{167}	+.54	69204	110%
82	16	Deletion 167	-.99	69207	N/A
83	17	Lys^{41}->Ala^{41}	+.25	69208	81%
84	18	His^{44}->Lys^{44}	-1.53	69212	70%
85	19	Glu^{47}->Ala^{47}	+.14	69205	0%
86	20	Arg^{23}->Ala^{23}	-.03	69206	31%
87	21	Lys^{24}->Ala^{24}	+1.95	69213	0%
88	22	Glu^{20}->Ala^{20}	-0.07	69211	0%
89	23	Asp^{28}->Ala^{28}	-.30	69210	147%
90	24	Met^{127}->Glu^{127}	N/A	69223	N/A
91	25	Met^{138}->Glu^{138}	N/A	69222	N/A
92	26	Met^{127}->Leu^{127}	N/A	69198	N/A
93	27	Met^{138}->Leu^{138}	N/A	69199	N/A
94	28	Cys^{18}->Ala^{18}	N/A	69188	N/A
95	29	$Gln^{12,21}$->$Glu^{12,21}$	N/A	69194	N/A
96	30	$Gln^{12,21,68}$->$Glu^{12,21,68}$	N/A	69195	N/A
97	31	Glu^{20}->Ala^{20}; Ser^{13}	+1.74	69209	0%

Table 5 Con't

Seq. ID	Variant	Analog	Relative HPLC Peak	ATCC No.	% Normal G-CSF Activity
		->Gly^{13}			
98	32	$Met^{127,138}$->$Leu^{127,138}$	+1.43	69200	98%
99	33	Ser^{13}->Ala^{13}	0	69221	110%
100	34	Lys^{17}->Ala^{17}	+.50	69226	70%
101	35	Gln^{121}->Ala^{121}	+2.7	69225	100%
102	36	Gln^{21}->Ala^{21}	+0.63	69217	9.6%
103	37	His^{44}->Ala^{44}	+1.52	69215	10.8%
104	38	His^{53}->Ala^{53}	+0.99	69219	8.3%
105	39	Asp^{110}->Ala^{110}	+1.97	69216	29%
106	40	Asp^{113}->Ala^{113}	-0.34	69218	0%
107	41	Thr^{117}->Ala^{117}	+0.4	69214	9.7%
108	42	Asp^{28}->Ala^{28}; Asp^{110} Ala^{110}	+3.2	69220	20.6%

Table 5 Con't

Seq. ID	Variant	Analog	Relative HPLC Peak	ATCC No.	% Normal G-CSF Activity
109	43	Glu^{124}->Ala^{124}	+0.16	69224	75%
110	44	Phe^{114}->Val^{114}, T^{117}->A^{117}**	+0.53		0%

**This analog was apparently a result of an inadvertent error in the oligo which was used to prepare number 41, above (Thr^{117}->Ala^{117}), and thus was prepared identically to the process used for that analog.

"N/A" indicates data which are not available.

1. Identification of Structure-Function Relationships

The first step used to design the present analogs was to determine what moieties are necessary for structural integrity of the G-CSF molecule. This was done at the amino acid residue level, although the

atomic level is also available for analysis. Modification of the residues necessary for structural integrity results in change in the overall structure of the G-CSF molecule. This may or may not be desirable, depending on the analog one wishes to produce. The working examples here were designed to maintain the overall structural integrity of the G-CSF molecule, for the purpose of maintain G-CSF receptor binding of the analog to the G-CSF receptor (as used in this section below, the "G-CSF receptor" refers to the natural G-CSF receptor, found on hematopoietic cells). It was assumed, and confirmed by the studies presented here, that G-CSF receptor binding is a necessary step for at least one biological activity, as determined by the above biological assays.

As can be seen from the figures, G-CSF (here, recombinant human met-G-CSF) is an antiparallel 4-alpha helical bundle with a left-handed twist, and with overall dimensions of 45 Å x 30Å x 24Å. The four helices within the bundle are referred to as helices A, B, C and D, and their connecting loops are known as the AB, BC and CD loops. The helix crossing angles range from -167.5° to -159.4°. Helices A, B, and C are straight, whereas helix D contains two kinds of structural characteristics, at Gly 150 and Ser 160 (of the recombinant human met-G-CSF). Overall, the G-CSF molecules is a bundle of four helices, connected in series by external loops. This structural information was then correlated with known functional information. It was known that residues (including methionine at position 1) 47, 23, 24, 20, 21, 44, 53, 113, 110, 28 and 114 may be modified, and the effect on biological activity would be substantial.

The majority of single mutations which lowered biological activity were centered around two regions of G-CSF that are separated by 30Å, and are located on different faces of the four helix bundle. One region involves interactions between the A helix and the D helix. This is further confirmed by the presence of salt bridges in the non-altered molecule as follows:

Atom	Helix	Atom	Helix	Distance
Arg 170 N1	D	Tyr 166 OH	A	3.3
Tyr 166 OH	D	Arg 23 N2	A	3.3
Glu 163 OE1	D	Arg 23 N1	A	2.8
Arg 23 N1	A	Gln 26 OE1	A	3.1
Gln 159 NE2	D	Gln 26 O	A	3.3

Distances reported here were for molecule A, as indicated in FIGURE 5 (wherein three G-CSF molecules crystallized together and were designated as A, B, and C). As can be seen, there is a web of salt bridges between helix A and helix D, which act to stabilize the helix A structure, and therefore affect the overall structure of the G-CSF molecule.

The area centering around residues Glu 20, Arg 23 and Lys 24 are found on the hydrophilic face of the A helix (residues 20-37). Substitution of the residues with the non-charged alanine residue at positions 20 and 23 resulted in similar HPLC retention times, indicating similarity in structure. Alteration of these sites altered the biological activity (as indicated by the present assays). Substitution at Lys 24 altered biological activity, but did not result in a similar HPLC retention time as the other two alterations.

The second site at which alteration lowered biological activity involves the AB helix. Changing glutamine at position 47 to alanine (analog no. 19, above) reduced biological activity (in the thymidine uptake assay) to zero. The AB helix is predominantly hydrophobic, except at the amino and carboxy termini; it contains one turn of a 3^{10} helix. There are two histadines at each termini (His 44 and His 56) and an additional glutamate at residue 46 which has the potential to form a salt bridge to His 44. The fourier transformed infra red spectrographic analysis (FTIR) of the analog suggests this analog is structurally similar to the non-altered recombinant G-CSF molecule. Further testing showed that this analog would not crystallize under the same conditions as the non-altered recombinant molecule.

Alterations at the carboxy terminus (Gln 174, Arg 167 and Arg 170) had little effect on biological activity. In contrast, deletion of the last eight residues (167-175) lowered biological activity. These results may indicate that the deletion destabilizes the overall structure which prevents the mutant from proper binding to the G-CSF receptor (and thus initiating signal transduction).

Generally, for the G-CSF internal core -- the internal four helix bundle lacking the external loops --the hydrophobic internal residues are essential for structural integrity. For example, in helix A, the internal hydrophobic residues are (with methionine being position 1) Phe 14, Cys 18, Val 22, Ile 25, Ile 32 and Leu 36. Generally, for the G-CSF internal core -- the internal four helix bundle lacking the external loops --the hydrophobic internal residues are essential for structural integrity. For example, in helix A, the internal hydrophobic residues are (with methionine being position 1 as in FIGURE 1) Phe 14, Cys 18, Val 22, Ile 25, Ile 32 and Leu 36. The other hydrophobic residues (again with the met at position 1) are: helix B, Ala 72,

Leu 76, Leu 79, Leu 83, Tyr 86, Leu 90 Leu 93; helix C, Leu 104, Leu 107, Val 111, Ala 114, Ile 118, Met 122; and helix D, Val 154, Val 158, Phe 161, Val 164, Val 168, Leu 172.

The above biological activity data, from the presently prepared G-CSF analogs, demonstrate that modification of the external loops interfere least with G-CSF overall structure. Preferred loops for analog prepration are the AB loop and the CD loop. The loops are relatively flexible structures as compared to the helices. The loops may contribute to the proteolysis of the molecule. G-CSF is relatively fast acting in vivo as the purpose the molecule serves is to generate a response to a biological challenge, i.e., selectively stimulate neutrophils. The G-CSF turnover rate is also relatively fast. The flexibility of the loops may provide a "handle" for proteases to attach to the molecule to inactivate the molecule. Modification of the loops to prevent protease degradation, yet have (via retention of the overall structure of non-modified G-CSF) no loss in biological activity may be accomplished.

This phenomenon is probably not limited to the G-CSF molecule but may also be common to the other molecules with known similar overall structures, as presented in Figure 2. Alteration of the external loop of, for example hGH, Interferon B, IL-2, GM-CSF and IL-4 may provide the least change to the overall structure. The external loops on the GM-CSF molecule are not as flexible as those found on the G-CSF molecule, and this may indicate a longer serum life, consistent with the broader biological activity of GM-CSF. Thus, the external loops of GM-CSF may be modified by releasing the external loops from the beta-sheet structure, which may make the loops more flexible (similar to those G-CSF) and therefore make the molecule more susceptible to protease degradation (and thus increase the turnover rate).

Alteration of these external loops may be effected by stabilizing the loops by connection to one or more of the internal helices. Connecting means are known to those in the art, such as the formation of a beta sheet, salt bridge, disulfide bonding or hydrophobic interactions, and other means are available. Also, deletion of one or more moieties, such as one or more amino acid residues or portions thereof, to prepare an abbreviated molecule and thus eliminate certain portions of the external loops may be effected.

Thus, by alteration of the external loops, preferably the AB loop (amino acids 58-72 of r-hu-met G-CSF) or the CD loop (amino acids 119 to 145 of r-hu-met-G-CSF), and less preferably the amino terminus (amino acids 1-10), one may therefore modify the biological function without elimination of G-CSF G-CSF receptor binding. For example, one may: (1) increase half-life (or prepare an oral dosage form, for example) of the G-CSF molecule by, for example, decreasing the ability of proteases to act on the G-CSF molecule or adding chemical modifications to the G-CSF molecule, such as one or more polyethylene glycol molecules or enteric coatings for oral formulation which would act to change some characteristic of the G-CSF molecule as described above, such as increasing serum or other half-life or decreasing antigenicity; (2) prepare a hybrid molecule, such as combining G-CSF with part or all of another protein such as another cytokine or another protein which effects signal transduction via entry through the cell through a G-CSF G-CSF receptor transport mechanism; or (3) increase the biological activity as in, for example, the ability to selectively stimulate neutrophils (as compared to a non-modified G-CSF molecule). This list is not limited to the above exemplars.

Another aspect observed from the above data is that stabilizing surface interactions may affect biological activity. This is apparent from comparing analogs 23 and 40. Analog 23 contains a substitution of the charged asparagine residue at position 28 for the neutrally-charged alanine residue in that position, and such substitution resulted in a 50% increase in the biological activity (as measured by the disclosed thymidine uptake assays). The asparagine residue at position 28 has a surface interaction with the asparagine residue at position 113; both residues being negatively charged, there is a certain amount of instability (due to the repelling of like charged moieties). When, however the asparagine at position 113 is replaced with the neutrally-charged alanine, the biological activity drops to zero (in the present assay system). This indicates that the asparagine at position 113 is critical to biological activity, and elimination of the asparagine at position 28 serves to increase the effect that asparagine at position 113 possesses.

The domains required for G-CSF receptor binding were also determined based on the above analogs prepared and the G-CSF structure. The G-CSF receptor binding domain is located at residues (with methionine being position 1) 11-57 (between the A and AB helix) and 100-118 (between the B and C helices). One may also prepare abbreviated molecules capable of binding to a G-CSF receptor and initiate signal transduction for selectively stimulating neutrophils by changing the external loop structure and having the receptor binding domains remain intact.

Residues essential for biological activity and presumably G-CSF receptor binding or signal transduction have been identified. Two distinct sites are located on two different regions of the secondary structure. What is here called "Site A" is located on a helix which is constrained by salt bridge contacts between two other members of the helical bundle. The second site, "Site B" is located on a relatively more flexible helix, AB. The AB helix is potentially more sensitive to local pH changes because of the type and position of the

residues at the carboxy and amino termini. The functional importance of this flexible helix may be important in a conformationally induced fit when binding to the G-CSF receptor. Additionally, the extended portion of the D helix is also indicated to be a G-CSF receptor binding domain, as ascertained by direct mutational and indirect comparative protein structure analysis. Deletion of the carboxy terminal end of r-hu-met-G-CSF reduces activity as it does for hGH, see, Cunningham and Wells, Science 244: 1081-1084 (1989). Cytokines which have similar structures, such as IL-6 and GM-CSF with predicted similar topology also center their biological activity along the carboxy end of the D helix, see Bazan, Immunology Today 11: 350-354 (1990)

A comparison of the structures and the positions of G-CSF receptor binding determinants between G-CSF and hGH suggests both molecules have similar means of signal transduction. Two separate G-CSF receptor binding sites have been identified for hGH De Vos et al., Science 255: 306-32 (1991). One of these binding sites (called "Site I") is formed by residues on the exposed faces of hGH's helix 1, the connection region between helix 1 and 2, and helix 4. The second binding site (called "Site II") is formed by surface residues of helix 1 and helix 3.

The G-CSF receptor binding determinates identified for G-CSF are located in the same relative positions as those identified for hGH. The G-CSF receptor binding site located in the connecting region between helix A and B on the AB helix (Site A) is similar in position to that reported for a small piece of helix (residues 38-47) of hGH. A single point mutation in the AB helix of G-CSF significantly reduces biological activity (as ascertained in the present assays), indicating the role in a G-CSF receptor-ligand interface. Binding of the G-CSF receptor may destabilize the 3^{10} helical nature of this region and induce a conformation change improving the binding energy of the ligand/G-CSF receptor complex.

In the hGH receptor complex, the first helix of the bundle donates residues to both of the binding sites required to dimerize the hGH receptor Mutational analysis of the corresponding helix of G-CSF (helix A) has identified three residues which are required for biological activity. Of these three residues, Glu 20 and Arg 24 lie on one face of the helical bundle towards helix C, whereas the side chain of Arg 23 (in two of the three molecules in the asymmetric unit) points to the face of the bundle towards helix D. The position of side chains of these biologically important residues indicates that similar to hGH, G-CSF may have a second G-CSF receptor binding site along the interface between helix A and helix C. In contrast with the hGH molecule, the amino terminus of G-CSF has a limited biological role as deletion of the first 11 residues has little effect on the biological activity.

As indicated above (see FIGURE 2, for example), G-CSF has a topological similarity with other cytokines. A correlation of the structure with previous biochemical studies, mutational analysis and direct comparison of specific residues of the hGH receptor complex indicates that G-CSF has two receptor binding sites. Site A lies along the interface of the A and D helices and includes residues in the small AB helix. Site B also includes residues in the A helix but lies along the interface between helices A and C. The conservation of structure and relative positions of biologically important residues between G-CSF and hGH is one indication of a common method of signal transduction in that the receptor is bound in two places. It is therefore found that G-CSF analogs possessing altered G-CSF receptor binding domains may be prepared by alteration at either of the G-CSF receptor binding sites (residues 20-57 and 145-175).

Knowledge of the three dimensional structure and correlation of the composition of G-CSF protein makes possible a systematic, rational method for preparing G-CSF analogs. The above working examples have demonstrated that the limitations of the size and polarity of the side chains within the core of the structure dictate how much change the molecule can tolerate before the overall structure is changed.

SEQUENCE LISTING

(1) GENERAL INFORMATION:

(i) APPLICANT: Amgen Inc.

(ii) TITLE OF INVENTION: G-CSF ANALOG COMPOSITIONS AND METHODS

(iii) NUMBER OF SEQUENCES: 110

(iv) CORRESPONDENCE ADDRESS:
(A) ADDRESSEE: Amgen Inc.
(B) STREET: Amgen Center, 1840 DeHavilland Drive
(C) CITY: Thousand Oaks
(D) STATE: California
(E) COUNTRY: United States of America
(F) ZIP: 91320-1789

(v) COMPUTER READABLE FORM:
(A) MEDIUM TYPE: Floppy disk
(B) COMPUTER: IBM PC compatible
(C) OPERATING SYSTEM: PC-DOS/MS-DOS

(2) INFORMATION FOR SEQ ID NO:1:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 565 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 30..554

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:1:

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TCTAGAAAAA ACCAAGGAGG TAATAAATA ATG ACT CCA TTA GGT CCT GCT TCT        53
                                Met Thr Pro Leu Gly Pro Ala Ser
                                  1               5

TCT CTG CCG CAA AGC TTT CTG CTG AAA TGT CTG GAA CAG GTT CGT AAA       101
Ser Leu Pro Gln Ser Phe Leu Leu Lys Cys Leu Glu Gln Val Arg Lys
     10                  15                  20

ATC CAG GGT GAC GGT GCT GCA CTG CAA GAA AAA CTG TGC GCT ACT TAC       149
Ile Gln Gly Asp Gly Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr Tyr
 25                  30                  35                  40
```

```
AAA CTG TGC CAT CCG GAA GAG CTG GTA CTG CTG GGT CAT TCT CTT GGG      197
Lys Leu Cys His Pro Glu Glu Leu Val Leu Leu Gly His Ser Leu Gly
                45                  50                  55

ATC CCG TGG GCT CCG CTG TCT TCT TGT CCA TCT CAA GCT CTT CAG CTG      245
Ile Pro Trp Ala Pro Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu
            60                  65                  70

GCT GGT TGT CTG TCT CAA CTG CAT TCT GGT CTG TTC CTG TAT CAG GGT      293
Ala Gly Cys Leu Ser Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly
        75                  80                  85

CTT CTG CAA GCT CTG GAA GGT ATC TCT CCG GAA CTG GGT CCG ACT CTG      341
Leu Leu Gln Ala Leu Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu
    90                  95                  100

GAC ACT CTG CAG CTA GAT GTA GCT GAC TTT GCT ACT ACT ATT TGG CAA      389
Asp Thr Leu Gln Leu Asp Val Ala Asp Phe Ala Thr Thr Ile Trp Gln
105                 110                 115                 120

CAG ATG GAA GAG CTC GGT ATG GCA CCA GCT CTG CAA CCG ACT CAA GGT      437
Gln Met Glu Glu Leu Gly Met Ala Pro Ala Leu Gln Pro Thr Gln Gly
                125                 130                 135

GCT ATG CCG GCA TTC GCT TCT GCA TTC CAG CGT CGT GCA GGA GGT GTA      485
Ala Met Pro Ala Phe Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly Val
            140                 145                 150

CTG GTT GCT TCT CAT CTG CAA TCT TTC CTG GAA GTA TCT TAC CGT GTT      533
Leu Val Ala Ser His Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val
        155                 160                 165

CTG CGT CAT CTG GCT CAG CCG TAATAGAATT C                            565
Leu Arg His Leu Ala Gln Pro
    170                 175
```

(2) INFORMATION FOR SEQ ID NO:2:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 175 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:2:

```
Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu
 1               5                  10                  15

Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu
            20                  25                  30

Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu
        35                  40                  45
```

Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
50 55 60

Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
65 70 75 80

Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
85 90 95

Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
100 105 110

Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala
115 120 125

Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
130 135 140

Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
145 150 155 160

Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro
165 170 175

(2) INFORMATION FOR SEQ ID NO:3:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 24 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:3:

CTTTCTGCTG CGTTGTCTGG AACA 24

(2) INFORMATION FOR SEQ ID NO:4:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 23 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:4:

ACAGGTTCGT CGTATCCAGG GTG 23

(2) INFORMATION FOR SEQ ID NO:5:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 23 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:5:

CACTGCAAGA ACGTCTGTGC GCT 23

(2) INFORMATION FOR SEQ ID NO:6:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 23 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:6:

CGCTACTTAC CGTCTGTGCC ATC 23

(2) INFORMATION FOR SEQ ID NO:7:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 24 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:7:

CTTTCTGCTG CGTTGTCTGG AACA 24

(2) INFORMATION FOR SEQ ID NO:8:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 23 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:8:

ACAGGTTCGT CGTATCCAGG GTG 23

(2) INFORMATION FOR SEQ ID NO:9:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 23 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:9:

CACTGCAAGA ACGTCTGTGC GCT 23

(2) INFORMATION FOR SEQ ID NO:10:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 24 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:10:

CTTTCTGCTG CGTTGTCTGG AACA 24

(2) INFORMATION FOR SEQ ID NO:11:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 23 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:11:

ACAGGTTCGT CGTATCCAGG GTG 23

(2) INFORMATION FOR SEQ ID NO:12:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 23 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:12:

CGCTACTTAC CGTCTGTCCC ATC 23

(2) INFORMATION FOR SEQ ID NO:13:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 24 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:13:

CTTTCTGCTG CGTTGTCTGG AACA 24

(2) INFORMATION FOR SEQ ID NO:14:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 23 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:14:

CACTGCAAGA ACGTCTGTGC GCT 23

(2) INFORMATION FOR SEQ ID NO:15:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 23 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:15:

CGCTACTTAC CGTCTGTGCC ATC 23

(2) INFORMATION FOR SEQ ID NO:16:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 23 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:16:

ACAGGTTCGT CGTATCCAGG GTG 23

(2) INFORMATION FOR SEQ ID NO:17:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 23 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:17:

CACTGCAAGA ACGTCTGTGC GCT 23

(2) INFORMATION FOR SEQ ID NO:18:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 23 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:18:

CGCTACTTAC CGTCTGTGCC ATC 23

(2) INFORMATION FOR SEQ ID NO:19:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 24 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:19:

CTTTCTGCTG CGTTGTCTGG AACA 24

(2) INFORMATION FOR SEQ ID NO:20:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 23 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:20:

ACAGGTTCGT CGTATCCAGG GTG 23

(2) INFORMATION FOR SEQ ID NO:21:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 23 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:21:

CACTGCAAGA ACGTCTGTGC GCT 23

(2) INFORMATION FOR SEQ ID NO:22:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 23 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:22:

CGCTACTTAC CGTCTGTGCC ATC 23

(2) INFORMATION FOR SEQ ID NO:23:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 23 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:23:

TCTGCTGAAA GCTCTGGAAC AGG 23

(2) INFORMATION FOR SEQ ID NO:24:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 23 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:24:

CTTGTCCATC TGAAGCTCTT CAG 23

(2) INFORMATION FOR SEQ ID NO:25:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 37 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:25:

GAAAAACTGT CCGCTACTTA CAAACTGTCC CATCCGG 37

(2) INFORMATION FOR SEQ ID NO:26:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 22 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:26:

TTCGTAAAAT CGCGGGTGAC GG 22

(2) INFORMATION FOR SEQ ID NO:27:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 22 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:27:

TCATCTGGCT GCGCCGTAAT AG 22

(2) INFORMATION FOR SEQ ID NO:28:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 22 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:28:

CCGTGTTCTG GCTCATCTGG CT 22

(2) INFORMATION FOR SEQ ID NO:29:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 24 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:29:

GAAGTATCTT ACGCTGTTCT GCGT 24

(2) INFORMATION FOR SEQ ID NO:30:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 25 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:30:

GAAGTATCTT ACTAAGTTCT GCGTC 25

(2) INFORMATION FOR SEQ ID NO:31:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 22 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:31:

CGCTACTTAC GCACTGTGCC AT 22

(2) INFORMATION FOR SEQ ID NO:32:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 22 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:32:

CAAACTGTGC AAGCCGGAAG AG 22

(2) INFORMATION FOR SEQ ID NO:33:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 22 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:33:

CATCCGGAAG CACTGGTACT GC 22

(2) INFORMATION FOR SEQ ID NO:34:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 23 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:34:

GGAACAGGTT GCTAAAATCC AGG 23

(2) INFORMATION FOR SEQ ID NO:35:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 25 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:35:

GAACAGGTTC GTGCGATCCA GGGTG 25

(2) INFORMATION FOR SEQ ID NO:36:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 22 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:36:

GAAATGTCTG GCACAGGTTC GT 22

(2) INFORMATION FOR SEQ ID NO:37:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 19 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:37:

TCCAGGGTGC CGGTGCTGC 19

(2) INFORMATION FOR SEQ ID NO:38:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 23 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:38:

AAGAGCTCGG TGAGGCACCA GCT 23

(2) INFORMATION FOR SEQ ID NO:39:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 23 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:39:

CTCAAGGTGC TGAGCCGGCA TTC 23

(2) INFORMATION FOR SEQ ID NO:40:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:40:

GAGCTCGGTC TGGCACCAGC 20

(2) INFORMATION FOR SEQ ID NO:41:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:41:

TCAAGGTGCT CTGCCGGCAT T 21

(2) INFORMATION FOR SEQ ID NO:42:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 23 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:42:

TCTGCCGCAA GCCTTTCTGC TGA 23

(2) INFORMATION FOR SEQ ID NO:43:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 24 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:43:

CTTTCTGCTG GCATGTCTGG AACA 24

(2) INFORMATION FOR SEQ ID NO:44:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 24 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:44:

CTATTTGGCA AGCGATGGAA GAGC 24

(2) INFORMATION FOR SEQ ID NO:45:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:45:

CAGATGGAAG CGCTCGGTAT G 21

(2) INFORMATION FOR SEQ ID NO:46:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:46:

GAGCTCGGTC TGGCACCAGC 20

(2) INFORMATION FOR SEQ ID NO:47:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:47:

TCAAGGTGCT CTGCCGGCAT T 21

(2) INFORMATION FOR SEQ ID NO:48:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 22 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:48:

GAAATGTCTG GCACAGGTTC GT 22

(2) INFORMATION FOR SEQ ID NO:49:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 19 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:49:

TTCCGGAGCG CACAGTTTG 19

(2) INFORMATION FOR SEQ ID NO:50:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 23 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:50:

CGAGAAGGCC TCGGGTGTCA AAC 23

(2) INFORMATION FOR SEQ ID NO:51:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 22 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:51:

ATGCCAAATT GCAGTAGCAA AG 22

(2) INFORMATION FOR SEQ ID NO:52:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 24 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:52:

ACAACGGTTT AACGTCATCG TTTC 24

(2) INFORMATION FOR SEQ ID NO:53:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 22 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:53:

ATCAGCTACT GCTAGCTGCA GA 22

(2) INFORMATION FOR SEQ ID NO:54:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 23 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:54:

TCAGTCGATG ACGATCGACG TCT 23

(2) INFORMATION FOR SEQ ID NO:55:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 22 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:55:

TTACGAACCG CTTCCAGACA TT 22

(2) INFORMATION FOR SEQ ID NO:56:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 25 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:56:

TAAAATGCTT GGCGAAGGTC TGTAA 25

(2) INFORMATION FOR SEQ ID NO:57:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 22 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:57:

GTAGCAAATG CAGCTACATC TA 22

(2) INFORMATION FOR SEQ ID NO:58:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 25 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:58:

CATCATCGTT TACGTCGATG TAGAT 25

(2) INFORMATION FOR SEQ ID NO:59:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:59:

CCAAGAGAAG CACCCAGCAG 20

(2) INFORMATION FOR SEQ ID NO:60:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 22 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:60:

AGGGTTCTCT TCGTGGGTCG TC 22

(2) INFORMATION FOR SEQ ID NO:61:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:61:

CACTGGCGGT GATAATGAGC 20

(2) INFORMATION FOR SEQ ID NO:62:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 19 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:62:

CTAGGCCAGG CATTACTGG 19

(2) INFORMATION FOR SEQ ID NO:63:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:63:

CCACTGGCGG TGATACTGAG C 21

(2) INFORMATION FOR SEQ ID NO:64:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 33 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:64:

AGCAGAAAGC TTTCCGGCAG AGAAGAAGCA GGA 33

(2) INFORMATION FOR SEQ ID NO:65:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 54 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:65:

GCCGCAAAGC TTTCTGCTGA AATGTCTGGA AGAGGTTCGT AAAATCCAGG GTGA 54

(2) INFORMATION FOR SEQ ID NO:66:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 59 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:66:

CTGGAATGCA GAAGCAAATG CCGGCATAGC ACCTTCAGTC GGTTGCAGAG CTGGTGCCA 59

(2) INFORMATION FOR SEQ ID NO:67:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 175 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:67:

```
Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu
 1               5                  10                  15

Arg Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu
            20                  25                  30

Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu
        35                  40                  45

Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
    50                  55                  60

Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
65                  70                  75                  80

Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
                85                  90                  95

Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
            100                 105                 110

Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala
        115                 120                 125

Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
    130                 135                 140

Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
145                 150                 155                 160

Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro
                165                 170                 175
```

(2) INFORMATION FOR SEQ ID NO:68:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 175 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:68:

```
Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu
 1               5                  10                  15

Lys Cys Leu Glu Gln Val Arg Arg Ile Gln Gly Asp Gly Ala Ala Leu
            20                  25                  30
```

```
Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu
          35                  40                  45

Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
     50                  55                  60

Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
 65                  70                  75                  80

Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
                 85                  90                  95

Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
            100                 105                 110

Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala
        115                 120                 125

Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
    130                 135                 140

Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
145                 150                 155                 160

Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro
                165                 170                 175
```

(2) INFORMATION FOR SEQ ID NO:69:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 175 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:69:

```
Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu
 1               5                  10                  15

Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu
            20                  25                  30

Gln Glu Arg Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu
        35                  40                  45

Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
    50                  55                  60

Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
65                  70                  75                  80

Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
                85                  90                  95
```

```
Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
            100                 105                 110

Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala
        115                 120                 125

Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
    130                 135                 140

Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
145                 150                 155                 160

Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro
                165                 170                 175
```

(2) INFORMATION FOR SEQ ID NO:70:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 175 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:70:

```
Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu
 1               5                  10                  15

Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu
            20                  25                  30

Gln Glu Lys Leu Cys Ala Thr Tyr Arg Leu Cys His Pro Glu Glu Leu
        35                  40                  45

Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
    50                  55                  60

Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
65                  70                  75                  80

Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
                85                  90                  95

Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
            100                 105                 110

Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala
        115                 120                 125

Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
    130                 135                 140

Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
145                 150                 155                 160
```

Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro
165 170 175

(2) INFORMATION FOR SEQ ID NO:71:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 175 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:71:

Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu
1 5 10 15

Arg Cys Leu Glu Gln Val Arg Arg Ile Gln Gly Asp Gly Ala Ala Leu
20 25 30

Gln Glu Arg Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu
35 40 45

Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
50 55 60

Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
65 70 75 80

Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
85 90 95

Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
100 105 110

Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala
115 120 125

Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
130 135 140

Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
145 150 155 160

Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro
165 170 175

(2) INFORMATION FOR SEQ ID NO:72:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 175 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:72:

```
Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu
 1               5                  10                  15

Arg Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu
            20                  25                  30

Gln Glu Arg Leu Cys Ala Thr Tyr Arg Leu Cys His Pro Glu Glu Leu
        35                  40                  45

Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
    50                  55                  60

Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
65                  70                  75                  80

Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
                85                  90                  95

Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
            100                 105                 110

Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala
        115                 120                 125

Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
    130                 135                 140

Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
145                 150                 155                 160

Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro
                165                 170                 175
```

(2) INFORMATION FOR SEQ ID NO:73:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 175 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:73:

```
Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu
 1               5                  10                  15

Lys Cys Leu Glu Gln Val Arg Arg Ile Gln Gly Asp Gly Ala Ala Leu
            20                  25                  30

Gln Glu Arg Leu Cys Ala Thr Tyr Arg Leu Cys His Pro Glu Glu Leu
        35                  40                  45
```

```
Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
 50                  55                  60

Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
65                  70                  75                  80

Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
                85                  90                  95

Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
            100                 105                 110

Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala
        115                 120                 125

Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
    130                 135                 140

Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
145                 150                 155                 160

Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro
                165                 170                 175
```

(2) INFORMATION FOR SEQ ID NO:74:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 175 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:74:

```
Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu
 1               5                  10                  15

Arg Cys Leu Glu Gln Val Arg Arg Ile Gln Gly Asp Gly Ala Ala Leu
            20                  25                  30

Gln Glu Arg Leu Cys Ala Thr Tyr Arg Leu Cys His Pro Glu Glu Leu
        35                  40                  45

Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
    50                  55                  60

Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
65                  70                  75                  80

Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
                85                  90                  95

Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
            100                 105                 110
```

```
Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala
        115                 120                 125

Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
    130                 135                 140

Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
145                 150                 155                 160

Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro
                165                 170                 175
```

(2) INFORMATION FOR SEQ ID NO:75:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 175 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:75:

```
Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu
  1               5                  10                  15

Arg Cys Leu Glu Gln Val Arg Arg Ile Gln Gly Asp Gly Ala Ala Leu
            20                  25                  30

Gln Glu Lys Leu Cys Ala Thr Tyr Arg Leu Cys His Pro Glu Glu Leu
        35                  40                  45

Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
    50                  55                  60

Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
65                  70                  75                  80

Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
                85                  90                  95

Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
            100                 105                 110

Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala
        115                 120                 125

Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
    130                 135                 140

Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
145                 150                 155                 160

Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro
                165                 170                 175
```

(2) INFORMATION FOR SEQ ID NO:76:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 175 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:76:

```
Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu
 1               5                  10                  15
Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu
            20                  25                  30

Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu
        35                  40                  45

Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
    50                  55                  60

Cys Pro Ser Glu Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
65                  70                  75                  80

Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
                85                  90                  95

Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
            100                 105                 110

Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala
        115                 120                 125

Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
    130                 135                 140

Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
145                 150                 155                 160

Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro
                165                 170                 175
```

(2) INFORMATION FOR SEQ ID NO:77:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 175 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:77:

```
Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu
 1               5                  10                  15

Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu
            20                  25                  30

Gln Glu Lys Leu Ser Ala Thr Tyr Lys Leu Ser His Pro Glu Glu Leu
        35                  40                  45

Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
    50                  55                  60

Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
65                  70                  75                  80

Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
                85                  90                  95

Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
            100                 105                 110

Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala
        115                 120                 125

Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
    130                 135                 140

Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
145                 150                 155                 160

Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro
                165                 170                 175
```

(2) INFORMATION FOR SEQ ID NO:78:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 175 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:78:

```
Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu
 1               5                  10                  15

Lys Cys Leu Glu Gln Val Arg Lys Ile Ala Gly Asp Gly Ala Ala Leu
            20                  25                  30

Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu
        35                  40                  45

Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
    50                  55                  60
```

```
Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
 65                  70                  75                  80

Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
                 85                  90                  95

Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
            100                 105                 110

Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala
        115                 120                 125

Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
    130                 135                 140

Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
145                 150                 155                 160

Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro
            165                 170                 175
```

(2) INFORMATION FOR SEQ ID NO:79:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 175 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:79:

```
Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu
 1               5                  10                  15

Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu
            20                  25                  30

Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu
        35                  40                  45

Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
    50                  55                  60

Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
65                  70                  75                  80

Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
                85                  90                  95

Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
            100                 105                 110

Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala
        115                 120                 125
```

```
Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
    130                 135                 140

Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
145                 150                 155                 160

Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Ala Pro
                165                 170                 175
```

(2) INFORMATION FOR SEQ ID NO:80:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 175 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:80:

```
Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu
 1               5                  10                  15

Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu
            20                  25                  30

Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu
        35                  40                  45

Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
    50                  55                  60

Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
65                  70                  75                  80

Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
                85                  90                  95

Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
            100                 105                 110

Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala
        115                 120                 125

Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
    130                 135                 140

Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
145                 150                 155                 160

Phe Leu Glu Val Ser Tyr Arg Val Leu Ala His Leu Ala Gln Pro
                165                 170                 175
```

(2) INFORMATION FOR SEQ ID NO:81:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 175 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:81:

```
Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu
 1               5                  10                  15

Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu
            20                  25                  30

Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu
        35                  40                  45

Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
    50                  55                  60

Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
65                  70                  75                  80

Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
                85                  90                  95

Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
            100                 105                 110

Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala
        115                 120                 125

Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
    130                 135                 140

Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
145                 150                 155                 160

Phe Leu Glu Val Ser Tyr Ala Val Leu Arg His Leu Ala Gln Pro
                165                 170                 175
```

(2) INFORMATION FOR SEQ ID NO:82:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 174 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:82:

```
Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu
 1               5                  10                  15

Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu
            20                  25                  30

Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu
        35                  40                  45

Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
    50                  55                  60

Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
65                  70                  75                  80

Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
                85                  90                  95

Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
            100                 105                 110

Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala
        115                 120                 125

Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
    130                 135                 140

Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
145                 150                 155                 160

Phe Leu Glu Val Ser Tyr Val Leu Arg His Leu Ala Gln Pro
                165                 170             174
```

(2) INFORMATION FOR SEQ ID NO:83:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 175 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:83:

```
Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu
 1               5                  10                  15

Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu
            20                  25                  30

Gln Glu Lys Leu Cys Ala Thr Tyr Ala Leu Cys His Pro Glu Glu Leu
        35                  40                  45

Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
    50                  55                  60
```

```
Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
 65                  70                  75                  80

Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
                85                  90                  95

Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
            100                 105                 110

Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala
        115                 120                 125

Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
    130                 135                 140

Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
145                 150                 155                 160

Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro
                165                 170                 175
```

(2) INFORMATION FOR SEQ ID NO:84:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 175 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:84:

```
Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu
 1               5                  10                  15

Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu
            20                  25                  30

Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys Lys Pro Glu Glu Leu
        35                  40                  45

Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
    50                  55                  60

Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
65                  70                  75                  80

Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
                85                  90                  95

Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
            100                 105                 110

Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala
        115                 120                 125
```

Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
130 135 140

Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
145 150 155 160

Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro
165 170 175

(2) INFORMATION FOR SEQ ID NO:85:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 175 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:85:

Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu
1 5 10 15

Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu
20 25 30

Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Ala Leu
35 40 45

Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
50 55 60

Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
65 70 75 80

Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
85 90 95

Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
100 105 110

Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala
115 120 125

Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
130 135 140

Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
145 150 155 160

Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro
165 170 175

(2) INFORMATION FOR SEQ ID NO:86:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 175 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:86:

```
Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu
 1               5                  10                  15

Lys Cys Leu Glu Gln Val Ala Lys Ile Gln Gly Asp Gly Ala Ala Leu
            20                  25                  30

Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu
        35                  40                  45

Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
    50                  55                  60

Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
65                  70                  75                  80

Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
                85                  90                  95

Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
            100                 105                 110

Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala
        115                 120                 125

Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
    130                 135                 140

Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
145                 150                 155                 160

Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro
                165                 170                 175
```

(2) INFORMATION FOR SEQ ID NO:87:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 175 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:87:

```
Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu
 1               5                  10                  15

Lys Cys Leu Glu Gln Val Arg Ala Ile Gln Gly Asp Gly Ala Ala Leu
            20                  25                  30

Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu
        35                  40                  45

Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
    50                  55                  60

Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
65                  70                  75                  80

Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
                85                  90                  95

Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
            100                 105                 110

Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala
        115                 120                 125

Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
    130                 135                 140

Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
145                 150                 155                 160

Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro
                165                 170                 175
```

(2) INFORMATION FOR SEQ ID NO:88:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 175 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:88:

```
Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu
 1               5                  10                  15

Lys Cys Leu Ala Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu
            20                  25                  30

Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu
        35                  40                  45

Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
    50                  55                  60
```

```
Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
 65                  70                  75                  80

Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
                 85                  90                  95

Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
            100                 105                 110

Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala
        115                 120                 125

Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
    130                 135                 140

Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
145                 150                 155                 160

Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro
                165                 170                 175
```

(2) INFORMATION FOR SEQ ID NO:89:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 175 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:89:

```
Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu
 1               5                  10                  15

Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Ala Gly Ala Ala Leu
            20                  25                  30

Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu
        35                  40                  45

Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
    50                  55                  60

Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
65                  70                  75                  80

Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
                85                  90                  95

Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
            100                 105                 110

Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala
        115                 120                 125
```

Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
130 135 140

Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
145 150 155 160

Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro
165 170 175

(2) INFORMATION FOR SEQ ID NO:90:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 175 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:90:

Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu
1 5 10 15

Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu
20 25 30

Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu
35 40 45

Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
50 55 60

Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
65 70 75 80

Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
85 90 95

Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
100 105 110

Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Glu Ala
115 120 125

Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
130 135 140

Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
145 150 155 160

Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro
165 170 175

(2) INFORMATION FOR SEQ ID NO:91:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 175 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:91:

```
Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu
 1               5                  10                  15

Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu
            20                  25                  30

Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu
        35                  40                  45

Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
    50                  55                  60

Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
65                  70                  75                  80

Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
                85                  90                  95

Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
            100                 105                 110

Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala
        115                 120                 125

Pro Ala Leu Gln Pro Thr Gln Gly Ala Glu Pro Ala Phe Ala Ser Ala
    130                 135                 140

Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
145                 150                 155                 160

Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro
                165                 170                 175
```

(2) INFORMATION FOR SEQ ID NO:92:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 175 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:92:

```
Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu
 1               5                  10                  15

Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu
            20                  25                  30

Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu
        35                  40                  45

Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
    50                  55                  60

Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
65                  70                  75                  80

Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
                85                  90                  95

Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
            100                 105                 110

Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Leu Ala
        115                 120                 125

Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
    130                 135                 140

Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
145                 150                 155                 160

Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro
                165                 170                 175
```

(2) INFORMATION FOR SEQ ID NO:93:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 175 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:93:

```
Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu
 1               5                  10                  15

Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu
            20                  25                  30

Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu
        35                  40                  45

Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
    50                  55                  60
```

```
Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
 65                  70                  75                  80

Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
                 85                  90                  95

Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
            100                 105                 110

Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala
        115                 120                 125

Pro Ala Leu Gln Pro Thr Gln Gly Ala Leu Pro Ala Phe Ala Ser Ala
    130                 135                 140

Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
145                 150                 155                 160

Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro
                165                 170                 175
```

(2) INFORMATION FOR SEQ ID NO:94:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 175 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:94:

```
Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu
 1               5                  10                  15

Lys Ala Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu
            20                  25                  30

Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu
        35                  40                  45

Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
    50                  55                  60

Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
65                  70                  75                  80

Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
                85                  90                  95

Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
            100                 105                 110

Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala
        115                 120                 125
```

```
Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
    130                 135                 140

Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
145                 150                 155                 160

Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro
                165                 170                 175
```

(2) INFORMATION FOR SEQ ID NO:95:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 175 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:95:

```
Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Glu Ser Phe Leu Leu
 1               5                  10                  15

Lys Cys Leu Glu Glu Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu
            20                  25                  30

Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu
        35                  40                  45

Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
    50                  55                  60

Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
65                  70                  75                  80

Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
                85                  90                  95

Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
            100                 105                 110

Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala
        115                 120                 125

Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
    130                 135                 140

Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
145                 150                 155                 160

Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro
                165                 170                 175
```

(2) INFORMATION FOR SEQ ID NO:96:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 175 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:96:

```
Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Glu Ser Phe Leu Leu
 1               5                  10                  15

Lys Cys Leu Glu Glu Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu
            20                  25                  30

Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu
        35                  40                  45

Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
    50                  55                  60

Cys Pro Ser Glu Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
65                  70                  75                  80

Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
                85                  90                  95

Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
            100                 105                 110

Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala
        115                 120                 125

Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
    130                 135                 140

Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
145                 150                 155                 160

Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro
                165                 170                 175
```

(2) INFORMATION FOR SEQ ID NO:97:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 175 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:97:

```
Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Gly Phe Leu Leu
 1               5                  10                  15

Lys Cys Leu Ala Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu
            20                  25                  30

Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu
        35                  40                  45

Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
    50                  55                  60

Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
65                  70                  75                  80

Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
                85                  90                  95

Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
            100                 105                 110

Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala
        115                 120                 125

Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
    130                 135                 140

Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
145                 150                 155                 160

Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro
                165                 170                 175
```

(2) INFORMATION FOR SEQ ID NO:98:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 175 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:98:

```
Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu
 1               5                  10                  15

Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu
            20                  25                  30

Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu
        35                  40                  45
```

```
Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
 50                  55                  60

Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
 65                  70                  75                  80

Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
                 85                  90                  95

Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
            100                 105                 110

Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Leu Ala
        115                 120                 125

Pro Ala Leu Gln Pro Thr Gln Gly Ala Leu Pro Ala Phe Ala Ser Ala
    130                 135                 140

Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
145                 150                 155                 160

Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro
                165                 170                 175
```

(2) INFORMATION FOR SEQ ID NO:99:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 175 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:99:

```
Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ala Phe Leu Leu
 1               5                  10                  15

Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu
            20                  25                  30

Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu
        35                  40                  45

Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
    50                  55                  60

Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
65                  70                  75                  80

Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
                85                  90                  95

Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
            100                 105                 110
```

Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala
115 120 125

Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
130 135 140

Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
145 150 155 160

Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro
165 170 175

(2) INFORMATION FOR SEQ ID NO:100:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 175 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:100:

Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu
1 5 10 15

Ala Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu
20 25 30

Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu
35 40 45

Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
50 55 60

Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
65 70 75 80

Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
85 90 95

Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
100 105 110

Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala
115 120 125

Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
130 135 140

Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
145 150 155 160

Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro
165 170 175

(2) INFORMATION FOR SEQ ID NO:101:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 175 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:101:

```
Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu
 1               5                  10                  15

Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu
            20                  25                  30

Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu
        35                  40                  45

Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
    50                  55                  60

Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
65                  70                  75                  80

Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
                85                  90                  95

Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
            100                 105                 110

Asp Phe Ala Thr Thr Ile Trp Gln Ala Met Glu Glu Leu Gly Met Ala
        115                 120                 125

Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
    130                 135                 140

Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
145                 150                 155                 160

Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro
                165                 170                 175
```

(2) INFORMATION FOR SEQ ID NO:102:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 175 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:102:

```
Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu
 1               5                  10                  15

Lys Cys Leu Glu Ala Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu
            20                  25                  30

Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu
        35                  40                  45

Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
    50                  55                  60

Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
65                  70                  75                  80

Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
                85                  90                  95

Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
            100                 105                 110

Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala
        115                 120                 125

Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
    130                 135                 140

Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
145                 150                 155                 160

Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro
                165                 170                 175
```

(2) INFORMATION FOR SEQ ID NO:103:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 175 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:103:

```
Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu
 1               5                  10                  15

Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu
            20                  25                  30

Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys Ala Pro Glu Glu Leu
        35                  40                  45

Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
    50                  55                  60
```

```
Cys Pro Ser Gln Ala L u Gln Leu Ala Gly Cys Leu Ser Gln Leu His
 65                  70                  75                  80

Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
                 85                  90                  95

Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
            100                 105                 110

Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala
        115                 120                 125

Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
    130                 135                 140

Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
145                 150                 155                 160

Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro
                165                 170                 175
```

(2) INFORMATION FOR SEQ ID NO:104:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 175 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:104:

```
Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu
 1               5                  10                  15

Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu
            20                  25                  30

Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu
        35                  40                  45

Val Leu Leu Gly Ala Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
    50                  55                  60

Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
65                  70                  75                  80

Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
                85                  90                  95

Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
            100                 105                 110

Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala
        115                 120                 125
```

Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
130 135 140

Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
145 150 155 160

Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro
165 170 175

(2) INFORMATION FOR SEQ ID NO:105:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 175 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:105:

Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu
1 5 10 15

Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu
20 25 30

Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu
35 40 45

Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
50 55 60

Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
65 70 75 80

Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
85 90 95

Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Ala Val Ala
100 105 110

Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala
115 120 125

Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
130 135 140

Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
145 150 155 160

Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro
165 170 175

(2) INFORMATION FOR SEQ ID NO:106:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 175 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:106:

```
Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu
 1               5                  10                  15

Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu
            20                  25                  30

Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu
        35                  40                  45

Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
    50                  55                  60

Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
65                  70                  75                  80

Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
                85                  90                  95

Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
            100                 105                 110

Ala Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala
        115                 120                 125

Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
    130                 135                 140

Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
145                 150                 155                 160

Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro
                165                 170                 175
```

(2) INFORMATION FOR SEQ ID NO:107:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 175 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:107:

```
Met Thr Pro Leu Gly Pro Ala S r Ser Leu Pro Gln Ser Phe Leu Leu
 1               5                  10                  15

Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu
            20                  25                  30

Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu
        35                  40                  45

Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
    50                  55                  60

Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
65                  70                  75                  80

Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
                85                  90                  95

Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
            100                 105                 110

Asp Phe Ala Thr Ala Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala
        115                 120                 125

Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
    130                 135                 140

Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
145                 150                 155                 160

Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro
                165                 170                 175
```

(2) INFORMATION FOR SEQ ID NO:108:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 175 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:108:

```
Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu
 1               5                  10                  15

Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Ala Gly Ala Ala Leu
            20                  25                  30

Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu
        35                  40                  45

Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
    50                  55                  60
```

```
Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
 65                  70                  75                  80

Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
                 85                  90                  95

Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Ala Val Ala
            100                 105                 110

Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala
        115                 120                 125

Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
    130                 135                 140

Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
145                 150                 155                 160

Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro
                165                 170                 175
```

(2) INFORMATION FOR SEQ ID NO:109:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 175 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:109:

```
Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu
 1               5                  10                  15

Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu
            20                  25                  30

Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu
        35                  40                  45

Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
    50                  55                  60

Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
65                  70                  75                  80

Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
                85                  90                  95

Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
            100                 105                 110
```

```
Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Ala Leu Gly Met Ala
        115                 120                 125

Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
    130                 135                 140

Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
145                 150                 155                 160

Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro
                165                 170                 175
```

(2) INFORMATION FOR SEQ ID NO:110:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 175 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:110:

```
Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu
 1               5                  10                  15

Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu
            20                  25                  30

Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu
        35                  40                  45

Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
    50                  55                  60

Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
65                  70                  75                  80

Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
                85                  90                  95

Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
            100                 105                 110

Asp Val Ala Thr Ala Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala
        115                 120                 125

Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
    130                 135                 140

Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
145                 150                 155                 160

Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro
                165                 170                 175
```

Claims

1. A method for preparing a G-CSF analog comprising the steps of:
   (a) viewing information conveying the three dimensional structure of a G-CSF molecule;

(b) selecting from said viewed information at least one site on said G-CSF molecule for alteration;
(c) preparing a G-CSF molecule having such alteration; and
(d) optionally, testing such G-CSF molecule for a desired characteristic.

2. A computer based method for preparing a G-CSF analog comprising the steps of:
(a) providing computer expression of the three dimensional structure of a G-CSF molecule;
(b) selecting from said computer expression at least one site on said G-CSF molecule for alteration;
(c) preparing a G-CSF molecule having such alteration; and,
(d) optionally, testing such G-CSF molecule for a desired characteristic.

3. A method for preparing a G-CSF analog with the aid of a computer comprising:
(a) providing said computer with the means for displaying the three dimensional structure of a G-CSF molecule including displaying the composition of moieties of said G-CSF molecule, preferably displaying the three dimensional location of each amino acid, and more preferably displaying the three dimensional location of each atom of a G-CSF molecule;
(b) viewing said display;
(c) selecting a site on said display for alteration in the composition of said molecule or the location of a moiety; and
(d) preparing a G-CSF analog with such alteration.

4. A computer-based method for preparing a G-CSF analog comprising the steps of:
(a) viewing the three dimensional structure of a G-CSF molecule via a computer, said computer having been previously programmed (i) to express the coordinates of a G-CSF molecule in three dimensional space, and (ii) to allow for entry of information for alteration of said G-CSF expression and viewing thereof;
(b) selecting a site on said visual image of said G-CSF molecule for alteration;
(c) entering information for said alteration on said computer;
(d) viewing a three dimensional structure of said altered G-CSF molecule via said computer;
(e) optionally repeating steps (a)-(e) above;
(f) preparing a G-CSF analog with said alteration; and
(g) optionally testing said G-CSF analog for a desired characteristic.

5. In a computer-based apparatus for displaying the three dimensional structure of a molecule, the improvement comprising means for correlating said three dimensional structure of a G-CSF molecule with the composition of said G-CSF molecule.

6. A method for crystallization of a protein comprising the steps of:
(a) combining, optionally by automated means, aqueous aliquots of said protein with either (i) aliquots of a salt solution, each aliquot having a different concentration of salt; or (ii) aliquots of a precipitant solution, each aliquot having a different concentration of precipitant;
(b) selecting at least one of said combined aliquots, said selection based on the formation of precrystalline forms, or, if no precrystalline forms are so produced, increasing the protein starting concentration of said aqueous aliquots of protein and repeating step (a);
(c) after said salt or said precipitant concentration is selected, repeating step (a) with said previously unselected solution in the presence of said selected concentration; and,
(d) repeating step (b) and step (a) until a crystal of desired quality is obtained.

7. A method of claim 6 wherein each combination pursuant to step (a) is performed in a range of pH.

8. A method of claim 6 wherein said combining of step (a) is done in the presence of a nucleation initiation unit.

9. A G-CSF analog having an amino acid sequence different from that of Figure 1 in that:
(a) the N-terminal methionine is optional; and
(b) one or more of amino acids 58-72 (i) is substituted with one or more different amino acids or (ii) deleted; or (iii) chemically modified.

10. A G-CSF analog of claim 9 wherein said analog is more resistant to proteolysis than a G-CSF molecule of Figure 1.

11. A G-CSF analog of claim 10 wherein at least one of said amino acids is chemically modified by the addition of a polyethylene glycol molecule.

12. A G-CSF analog having an amino acid sequence different from that of Figure 1 in that:
(a) the N-terminal methionine is optional; and
(b) one or more of amino acids 119-125 (i) is substituted with one or more different amino acids or (ii) deleted; or (iii) chemically modified.

13. A G-CSF analog of claim 12 wherein said analog is more resistant to proteolysis than a G-CSF molecule of Figure 1.

14. A G-CSF analog of claim 12 wherein at least one of said amino acids is chemically modified by the addition of a polyethylene glycol molecule.

15. A G-CSF molecule having the AB loop stabilized by connecting such loop to one or more of helices A, B, C, or D.

16. A G-CSF molecule having the CD loop stabilized by connecting such loop to one or more of helices A, B, C, or D.

17. A G-CSF analog, optionally in a pharmaceutically effective carrier, optionally in a pharmaceutically effective carrier, wherein the amino acid sequence differs from that of Figure 1 in that Lys^{17}->Arg^{17} and the N-terminal methionine is optional.

18. A G-CSF analog, optionally in a pharmaceutically effective carrier, wherein the amino acid sequence differs from that of Figure 1 in that Lys^{35}->Arg^{35} and the N-terminal methionine is optional.

19. A G-CSF analog, optionally in a pharmaceutically effective carrier, wherein the amino acid sequence differs from that of Figure 1 in that Lys^{41}->Arg^{41} and the N-terminal methionine is optional.

20. A G-CSF analog, optionally in a pharmaceutically effective carrier, wherein the amino acid sequence differs from that of Figure 1 in that $Lys^{17,24,35}$->$Arg^{17,24,35}$ and the N-terminal methionine is optional.

21. A G-CSF analog, optionally in a pharmaceutically effective carrier, wherein the amino acid sequence differs from that of Figure 1 in that $Lys^{17,35,41}$->$Arg^{17,35,41}$ and the N-terminal methionine is optional.

22. A G-CSF analog, optionally in a pharmaceutically effective carrier, wherein the amino acid sequence differs from that of Figure 1 in that $Lys^{24,35,41}$->$Arg^{24,35,41}$ and the N-terminal methionine is optional.

23. A G-CSF analog, optionally in a pharmaceutically effective carrier, wherein the amino acid sequence differs from that of Figure 1 in that $Lys^{17,24,35,41}$ ->$Arg^{17,24,35,41}$ and the N-terminal methionine is optional.

24. A G-CSF analog, optionally in a pharmaceutically effective carrier, wherein the amino acid sequence differs from that of Figure 1 in that $Lys^{17,24,41}$->$Arg^{17,24,41}$ and the N-terminal methionine is optional.

25. A G-CSF analog, optionally in a pharmaceutically effective carrier, wherein the amino acid sequence differs from that of Figure 1 in that Gln^{68}->Glu^{68} and the N-terminal methionine is optional.

26. A G-CSF analog, optionally in a pharmaceutically effective carrier, wherein the amino acid sequence differs from that of Figure 1 in that $Cys^{37,43}$->$Ser^{37,43}$ and the N-terminal methionine is optional.

27. A G-CSF analog, optionally in a pharmaceutically effective carrier, wherein the amino acid sequence differs from that of Figure 1 in that Gln^{26}->Ala^{26} and the N-terminal methionine is optional.

28. A G-CSF analog, optionally in a pharmaceutically effective carrier, wherein the amino acid sequence differs from that of Figure 1 in that Gln^{174}->Ala^{174} and the N-terminal methionine is optional.

29. A G-CSF analog, optionally in a pharmaceutically effective carrier, wherein the amino acid sequence differs from that of Figure 1 in that Arg^{170}->Ala^{170} and the N-terminal methionine is optional.

30. A G-CSF analog, optionally in a pharmaceutically effective carrier, wherein the amino acid sequence differs from that of Figure 1 in that Arg^{167}->Ala^{167} and the N-terminal methionine is optional.

31. A G-CSF analog, optionally in a pharmaceutically effective carrier, wherein the amino acid sequence differs from that of Figure 1 in that there is a deletion at position 167 and the N-terminal methionine is optional.

32. A G-CSF analog, optionally in a pharmaceutically effective carrier, wherein the amino acid sequence differs from that of Figure 1 in that Lys^{41}->Ala^{41} and the N-terminal methionine is optional.

33. A G-CSF analog, optionally in a pharmaceutically effective carrier, wherein the amino acid sequence differs from that of Figure 1 in that His^{44}->Lys^{44} and the N-terminal methionine is optional.

34. A G-CSF analog, optionally in a pharmaceutically effective carrier, wherein the amino acid sequence differs from that of Figure 1 in that Glu^{47}->Ala^{47} and the N-terminal methionine is optional.

35. A G-CSF analog, optionally in a pharmaceutically effective carrier, wherein the amino acid sequence differs from that of Figure 1 in that Arg^{23}->Ala^{23} and the N-terminal methionine is optional.

36. A G-CSF analog, optionally in a pharmaceutically effective carrier, wherein the amino acid sequence differs from that of Figure 1 in that Lys^{24}->Ala^{24} and the N-terminal methionine is optional.

37. A G-CSF analog, optionally in a pharmaceutically effective carrier, wherein the amino acid sequence differs from that of Figure 1 in that Glu^{20}->Ala^{20} and the N-terminal methionine is optional.

38. A G-CSF analog, optionally in a pharmaceutically effective carrier, wherein the amino acid sequence differs from that of Figure 1 in that Asp^{28}->Ala^{28} and the N-terminal methionine is optional.

39. A G-CSF analog, optionally in a pharmaceutically effective carrier, wherein the amino acid sequence differs from that of Figure 1 in that Met^{127}->Glu^{127} and the N-terminal methionine is optional.

40. A G-CSF analog, optionally in a pharmaceutically effective carrier, wherein the amino acid sequence differs from tha of Figure 1 in that Met^{138}->Glu^{138} and the N-terminal methionine is optional.

41. A G-CSF analog, optionally in a pharmaceutically effective carrier, wherein the amino acid sequence differs from that of Figure 1 in that Met^{127}->Leu^{127} and the N-terminal methionine is optional.

42. A G-CSF analog, optionally in a pharmaceutically effective carrier, wherein the amino acid sequence differs from that of Figure 1 in that Met^{138}->Leu^{138} and the N-terminal methionine is optional.

43. A G-CSF analog, optionally in a pharmaceutically effective carrier, wherein the amino acid sequence differs from that of Figure 1 in that Cys^{18}->Ala^{18} and the N-terminal methionine is optional.

44. A G-CSF analog, optionally in a pharmaceutically effective carrier, wherein the amino acid sequence differs from that of Figure 1 in that $Gln^{12,21}$->$Glu^{12,21}$ and the N-terminal methionine is optional.

45. A G-CSF analog, optionally in a pharmaceutically effective carrier, wherein the amino acid sequence differs from that of Figure 1 in that $Gln^{12,21,68}$->$Glu^{12,21,68}$ and the N-terminal methionine is optional.

46. A G-CSF analog, optionally in a pharmaceutically effective carrier, wherein the amino acid sequence differs from that of Figure 1 in that Glu^{20}->Ala^{20}; Ser^{13}->Gly^{13} and the N-terminal methionine is optional.

47. A G-CSF analog, optionally in a pharmaceutically effective carrier, wherein the amino acid sequence differs from that of Figure 1 in that $Met^{127,138}$->$Leu^{127,138}$ and the N-terminal methionine is optional.

48. A G-CSF analog, optionally in a pharmaceutically effective carrier, wherein the amino acid sequence differs from that of Figure 1 in that Ser^{13}->Ala^{13} and the N-terminal methionine is optional.

49. A G-CSF analog, optionally in a pharmaceutically effective carrier, wherein the amino acid sequence differs from that of Figure 1 in that Lys^{17}->Ala^{17} and the N-terminal methionine is optional.

50. A G-CSF analog, optionally in a pharmaceutically effective carrier, wherein the amino acid sequence differs from that of Figure 1 in that Gln^{121}->Ala^{121} and the N-terminal methionine is optional.

51. A G-CSF analog, optionally in a pharmaceutically effective carrier, wherein the amino acid sequence differs from that of Figure 1 in that Gln^{21}->Ala^{21} and the N-terminal methionine is optional.

52. A G-CSF analog, optionally in a pharmaceutically effective carrier, wherein the amino acid sequence differs from that of Figure 1 in that His^{44}->Ala^{44} and the N-terminal methionine is optional.

53. A G-CSF analog, optionally in a pharmaceutically effective carrier, wherein said amino acid sequenc differs from that of Figure 1 in that His^{53}->Ala^{53} and the N-terminal methionine is optional.

54. A G-CSF analog, optionally in a pharmaceutically effective carrier, wherein the amino acid sequence differs from that of Figure 1 in that Asp^{110}->Ala^{110} and the N-terminal methionine is optional.

55. A G-CSF analog, optionally in a pharmaceutically effective carrier, wherein the amino acid sequence differs from that of Figure 1 in that Asp^{113}->Ala^{113} and the N-terminal methionine is optional.

56. A G-CSF analog, optionally in a pharmaceutically effective carrier, wherein the amino acid sequence differs from that of Figure 1 in that Thr^{117}->Ala^{117} and the N-terminal methionine is optional.

57. A G-CSF analog, optionally in a pharmaceutically effective carrier, wherein the amino acid sequence differs from that of Figure 1 in that Asp^{28}->Ala^{28}; Asp^{110} ->Ala^{110} and the N-terminal methionine is optional.

58. A G-CSF analog, optionally in a pharmaceutically effective carrier, wherein the amino acid sequence differs from that of Figure 1 in that Glu^{124}->Ala^{124} and the N-terminal methionine is optional.

59. A G-CSF analog, optionally in a pharmaceutically effective carrier, wherein the amino acid sequence differs from that of Figure 1 in that Phe^{114}->Val^{114}, Thr^{117}->A^{117} and the N-terminal methionine is optional.

60. The G-CSF analog DNA-containing plasmids and bacterial host cells transformed therewith available from the American Type Culture Collection under the accession numbers ATCC 69184, 69185, 69186, 69187, 69188, 69189, 69190, 69191, 69192, 69193, 69194, 69195, 69196, 69197, 69198, 69199, 69200, 69201, 69202, 69203, 69204, 69205, 69206, 69207, 69208, 69209, 69210, 69211, 69212, 69213, 69214, 69215, 69216, 69217, 69218, 69219, 69220, 69221, 69222, 69223, 69224, 69225 and 69226.

```
                                                Met Thr Pro Leu Gly Pro Ala
TCTAGAAAAAACCAAGGAGGTAATAAATA ATG ACT CCA TTA GGT CCT GCT

Ser Ser Leu Pro Gln Ser Phe Leu Leu Lys Cys Leu Glu Gln
TCT TCT CTG CCG CAA AGC TTT CTG CTG AAA TGT CTG GAA CAG

Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu Gln Glu Lys Leu
GTT CGT AAA ATC CAG GGT GAC GGT GCT GCA CTG CAA GAA AAA CTG

Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu Val Leu Leu
TGC GCT ACT TAC AAA CTG TGC CAT CCG GAA GAG CTG GTA CTG CTG

Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser Cys Pro
GGT CAT TCT CTT GGG ATC CCG TGG GCT CCG CTG TCT TCT TGT CCA

Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His Ser
TCT CAA GCT CTT CAG CTG GCT GGT TGT CTG TCT CAA CTG CAT TCT

Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
GGT CTG TTC CTG TAT CAG GGT CTT CTG CAA GCT CTG GAA GGT ATC

Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val
TCT CCG GAA CTG GGT CCG ACT CTG GAC ACT CTG CAG CTA GAT GTA

Ala Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly
GCT GAC TTT GCT ACT ACT ATT TGG CAA CAG ATG GAA GAG CTC GGT

Met Ala Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe
ATG GCA CCA GCT CTG CAA CCG ACT CAA GGT GCT ATG CCG GCA TTC

Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser
GCT TCT GCA TTC CAG CGT CGT GCA GGA GGT GTA CTG GTT GCT TCT

His Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His
CAT CTG CAA TCT TTC CTG GAA GTA TCT TAC CGT GTT CTG CGT CAT

Leu Ala Gln Pro OC  AM
CTG GCT CAG CCG TAA TAG AATTC
```

FIGURE 1

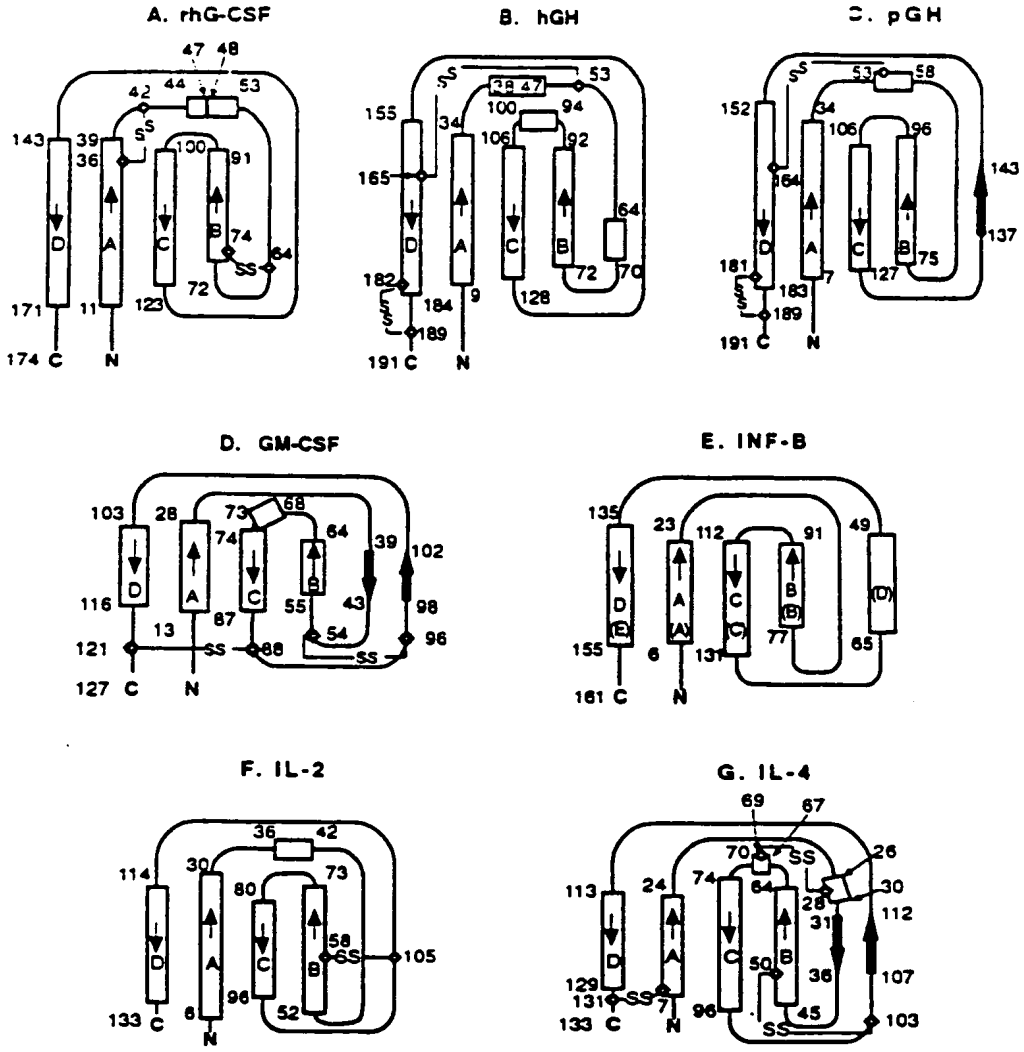

FIGURE 2

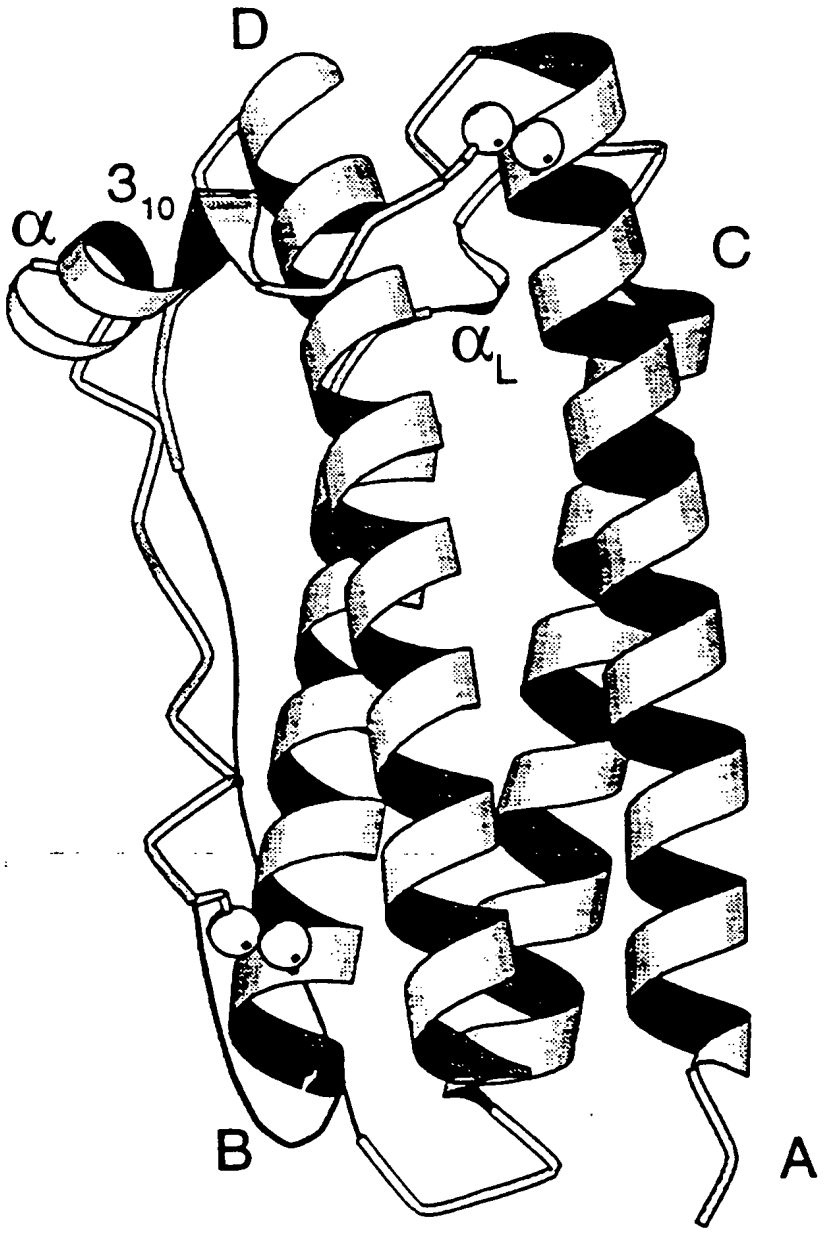

FIGURE 3

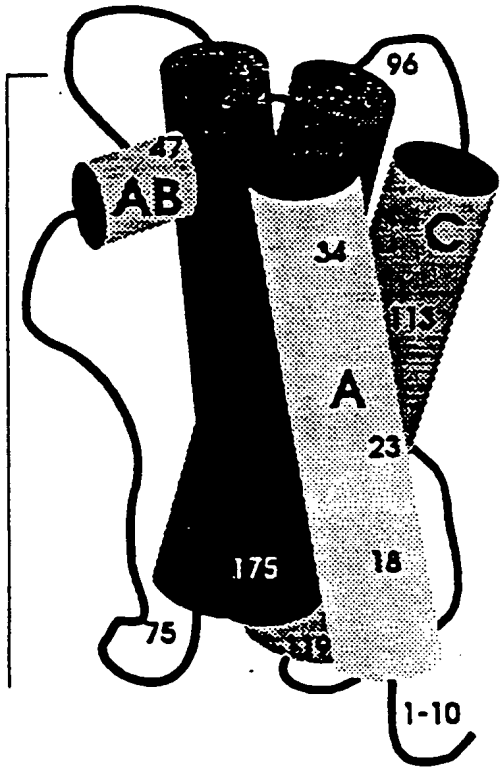

FIGURE 4

FIGURE 5

```
ATOM    1 CB  LEU   10     58.751  58.191 -14.868  1.00 61.22      A1
ATOM    2 CG  LEU   10     58.360  59.271 -13.939  1.00 60.19      A1
ATOM    3 CD1 LEU   10     59.307  60.461 -14.022  1.00 60.14      A1
ATOM    4 CD2 LEU   10     56.954  59.658 -14.335  1.00 60.68      A1
ATOM    5 C   LEU   10     60.544  56.734 -13.849  1.00 62.85      A1
ATOM    6 O   LEU   10     60.079  55.595 -14.041  1.00 63.08      A1
ATOM    7 1HT1 LEU   10     59.876  56.135 -15.998  1.00  0.00      A1
ATOM    8 1HT2 LEU   10     61.323  56.887 -16.434  1.00  0.00      A1
ATOM    9 N   LEU   10     60.328  57.059 -16.204  1.00 62.24      A1
ATOM   10 1HT3 LEU   10     59.817  57.535 -16.971  1.00  0.00      A1
ATOM   11 CA  LEU   10     60.183  57.758 -14.941  1.00 62.58      A1
ATOM   12 N   PRO   11     61.357  56.962 -12.780  1.00 61.96      A1
ATOM   13 CD  PRO   11     61.960  58.238 -12.383  1.00 61.21      A1
ATOM   14 CA  PRO   11     61.832  55.889 -11.906  1.00 61.34      A1
ATOM   15 CB  PRO   11     62.915  56.547 -11.043  1.00 59.77      A1
ATOM   16 CG  PRO   11     62.511  57.983 -10.975  1.00 59.16      A1
ATOM   17 C   PRO   11     60.712  55.225 -11.109  1.00 60.68      A1
ATOM   18 O   PRO   11     60.075  55.843 -10.250  1.00 61.73      A1
ATOM   19 N   GLN   12     60.466  53.946 -11.407  1.00 59.31      A1
ATOM   20 H   GLN   12     60.944  53.573 -12.175  1.00  0.00      A1
ATOM   21 CA  GLN   12     59.468  53.121 -10.743  1.00 57.22      A1
ATOM   22 CB  GLN   12     59.779  51.646 -10.970  1.00 59.27      A1
ATOM   23 CG  GLN   12     58.620  50.714 -10.591  1.00 59.70      A1
ATOM   24 CD  GLN   12     57.604  50.575 -11.702  1.00 61.71      A1
ATOM   25 OE1 GLN   12     57.170  49.465 -11.970  1.00 65.82      A1
ATOM   26 NE2 GLN   12     57.227  51.534 -12.541  1.00 63.02      A1
ATOM   27 1HE21 GLN   12     57.639  52.419 -12.489  1.00  0.00      A1
ATOM   28 1HE22 GLN   12     56.500  51.308 -13.156  1.00  0.00      A1
ATOM   29 C   GLN   12     59.336  53.347  -9.245  1.00 55.34      A1
ATOM   30 O   GLN   12     58.242  53.196  -8.708  1.00 54.56      A1
ATOM   31 N   SER   13     60.423  53.732  -8.576  1.00 53.44      A1
ATOM   32 H   SER   13     61.276  53.839  -9.033  1.00  0.00      A1
ATOM   33 CA  SER   13     60.335  53.974  -7.168  1.00 52.86      A1

ATOM   34 CB  SER   13     61.704  54.144  -6.626  1.00 52.24      A1
ATOM   35 OG  SER   13     61.702  53.493  -5.362  1.00 56.64      A1
ATOM   36 HG  SER   13     61.534  52.551  -5.477  1.00  0.00      A1
ATOM   37 C   SER   13     59.497  55.214  -6.900  1.00 52.58      A1
ATOM   38 O   SER   13     58.509  55.144  -6.160  1.00 53.55      A1
ATOM   39 N   PHE   14     59.791  56.333  -7.577  1.00 50.84      A1
ATOM   40 H   PHE   14     60.469  56.292  -8.279  1.00  0.00      A1
ATOM   41 CA  PHE   14     59.067  57.590  -7.423  1.00 47.21      A1
ATOM   42 CB  PHE   14     59.611  58.590  -8.454  1.00 44.68      A1
ATOM   43 CG  PHE   14     58.618  59.669  -8.866  1.00 42.88      A1
ATOM   44 CD1 PHE   14     58.052  59.594 -10.123  1.00 40.40      A1
ATOM   45 CD2 PHE   14     58.264  60.673  -7.978  1.00 40.30      A1
ATOM   46 CE1 PHE   14     57.114  60.518 -10.507  1.00 39.59      A1
ATOM   47 CE2 PHE   14     57.329  61.587  -8.380  1.00 41.82      A1
ATOM   48 CZ  PHE   14     56.751  61.515  -9.635  1.00 41.56      A1
ATOM   49 C   PHE   14     57.605  57.263  -7.661  1.00 45.83      A1

ATOM   50 O   PHE   14     56.789  57.588  -6.805  1.00 46.07      A1
ATOM   51 N   LEU   15     57.298  56.509  -8.718  1.00 44.64      A1
ATOM   52 H   LEU   15     58.024  56.183  -9.287  1.00  0.00      A1
ATOM   53 CA  LEU   15     55.940  56.121  -9.038  1.00 44.53      A1
ATOM   54 CB  LEU   15     55.858  55.402 -10.300  1.00 48.75      A1
ATOM   55 CG  LEU   15     54.853  56.013 -11.289  1.00 51.65      A1
ATOM   56 CD1 LEU   15     55.525  57.121 -12.105  1.00 50.33      A1
ATOM   57 CD2 LEU   15     54.320  54.906 -12.204  1.00 53.77      A1
ATOM   58 C   LEU   15     55.169  55.410  -8.014  1.00 44.07      A1
ATOM   59 O   LEU   15     53.945  55.567  -7.959  1.00 45.46      A1
ATOM   60 N   LEU   16     55.809  54.620  -7.166  1.00 43.18      A1
ATOM   61 H   LEU   16     56.781  54.503  -7.251  1.00  0.00      A1
ATOM   62 CA  LEU   16     55.110  53.913  -6.095  1.00 42.96      A1
ATOM   63 CB  LEU   16     55.866  52.623  -5.751  1.00 44.34      A1
ATOM   64 CG  LEU   16     55.840  51.608  -6.868  1.00 42.25      A1
ATOM   65 CD1 LEU   16     56.889  50.567  -6.596  1.00 43.68      A1
ATOM   66 CD2 LEU   16     54.413  51.068  -7.030  1.00 42.75      A1
ATOM   67 C   LEU   16     54.963  54.778  -4.852  1.00 42.35      A1
ATOM   68 O   LEU   16     54.077  54.579  -4.018  1.00 42.65      A1
ATOM   69 N   LYS   17     55.823  55.779  -4.703  1.00 42.47      A1
ATOM   70 H   LYS   17     56.587  55.840  -5.320  1.00  0.00      A1
ATOM   71 CA  LYS   17     55.681  56.767  -3.650  1.00 42.07      A1
ATOM   72 CB  LYS   17     56.995  57.554  -3.573  1.00 44.14      A1
ATOM   73 CG  LYS   17     57.214  58.197  -2.223  1.00 49.61      A1
ATOM   74 CD  LYS   17     57.114  57.164  -1.086  1.00 55.15      A1
ATOM   75 CE  LYS   17     56.747  57.804   0.293  1.00 62.05      A1
ATOM   76 NZ  LYS   17     55.462  58.533   0.331  1.00 65.48      A1
ATOM   77 1HZ1 LYS   17     54.684  57.884   0.098  1.00  0.00      A1
ATOM   78 1HZ2 LYS   17     55.482  59.308  -0.362  1.00  0.00      A1
ATOM   79 1HZ3 LYS   17     55.312  58.926   1.282  1.00  0.00      A1
ATOM   80 C   LYS   17     54.463  57.640  -4.051  1.00 41.20      A1
ATOM   81 O   LYS   17     53.648  57.999  -3.186  1.00 40.66      A1
ATOM   82 N   CYS   18     54.272  57.992  -5.346  1.00 39.14      A1
ATOM   83 H   CYS   18     54.998  57.809  -5.981  1.00  0.00      A1
ATOM   84 CA  CYS   18     53.030  58.656  -5.802  1.00 37.42      A1
ATOM   85 CB  CYS   18     53.092  58.891  -7.261  1.00 38.02      A1
ATOM   86 SG  CYS   18     54.421  60.026  -7.681  1.00 40.40      A1
ATOM   87 C   CYS   18     51.859  57.789  -5.502  1.00 39.33      A1
ATOM   88 O   CYS   18     50.959  58.346  -4.847  1.00 40.85      A1
ATOM   89 N   LEU   19     51.738  56.475  -5.842  1.00 37.15      A1
ATOM   90 H   LEU   19     52.462  56.038  -6.341  1.00  0.00      A1
ATOM   91 CA  LEU   19     50.521  55.702  -5.534  1.00 36.00      A1
ATOM   92 CB  LEU   19     50.644  54.204  -5.947  1.00 38.31      A1
ATOM   93 CG  LEU   19     49.410  53.271  -5.657  1.00 40.86      A1
ATOM   94 CD1 LEU   19     48.208  53.684  -6.467  1.00 39.71      A1
ATOM   95 CD2 LEU   19     49.692  51.833  -6.113  1.00 45.71      A1
ATOM   96 C   LEU   19     50.102  55.736  -4.076  1.00 34.52      A1
ATOM   97 O   LEU   19     48.930  55.949  -3.766  1.00 32.75      A1
ATOM   98 N   GLU   20     51.030  55.576  -3.166  1.00 31.88      A1
ATOM   99 H   GLU   20     51.940  55.338  -3.455  1.00  0.00      A1
ATOM  100 CA  GLU   20     50.750  55.710  -1.748  1.00 31.40      A1
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FIGURE 5

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ATOM  101 CB  GLU  20     52.053  55.334  -1.167  1.00 35.25      A1
ATOM  102 CG  GLU  20     52.508  55.504   0.260  1.00 43.21      A1
ATOM  103 CD  GLU  20     53.948  54.947   0.407  1.00 51.06      A1
ATOM  104 OE1 GLU  20     54.320  54.660   1.546  1.00 56.78      A1
ATOM  105 OE2 GLU  20     54.708  54.766  -0.570  1.00 51.57      A1
ATOM  106 C   GLU  20     50.230  57.117  -1.326  1.00 33.25      A1
ATOM  107 O   GLU  20     49.432  57.291  -0.380  1.00 33.30      A1
ATOM  108 N   GLN  21     50.660  58.167  -2.044  1.00 32.33      A1
ATOM  109 H   GLN  21     51.270  58.004  -2.794  1.00  0.00      A1
ATOM  110 CA  GLN  21     50.275  59.538  -1.742  1.00 31.00      A1
ATOM  111 CB  GLN  21     51.326  60.489  -2.340  1.00 32.37      A1
ATOM  112 CG  GLN  21     52.436  60.530  -1.272  1.00 38.01      A1
ATOM  113 CD  GLN  21     53.622  61.460  -1.504  1.00 42.67      A1
ATOM  114 OE1 GLN  21     54.008  62.236  -0.615  1.00 43.63      A1
ATOM  115 NE2 GLN  21     54.256  61.448  -2.678  1.00 42.31      A1
ATOM  116 HE21 GLN  21    53.965  60.840  -3.384  1.00  0.00      A1
ATOM  117 HE22 GLN  21    55.026  62.052  -2.730  1.00  0.00      A1
ATOM  118 C   GLN  21     48.894  59.765  -2.288  1.00 28.51      A1
ATOM  119 O   GLN  21     48.027  60.242  -1.563  1.00 28.65      A1
ATOM  120 N   VAL  22     48.682  59.319  -3.521  1.00 25.85      A1
ATOM  121 H   VAL  22     49.448  58.980  -4.013  1.00  0.00      A1
ATOM  122 CA  VAL  22     47.382  59.303  -4.161  1.00 24.94      A1
ATOM  123 CB  VAL  22     47.508  58.614  -5.526  1.00 24.09      A1
ATOM  124 CG1 VAL  22     46.154  58.378  -6.096  1.00 19.97      A1
ATOM  125 CG2 VAL  22     48.252  59.479  -6.498  1.00 25.82      A1
ATOM  126 C   VAL  22     46.418  58.549  -3.226  1.00 25.65      A1
ATOM  127 O   VAL  22     45.428  59.190  -2.800  1.00 29.31      A1
ATOM  128 N   ARG  23     46.643  57.291  -2.759  1.00 23.93      A1
ATOM  129 H   ARG  23     47.440  56.819  -3.056  1.00  0.00      A1
ATOM  130 CA  ARG  23     45.667  56.593  -1.892  1.00 20.67      A1
ATOM  131 CB  ARG  23     46.104  55.135  -1.635  1.00 20.45      A1
ATOM  132 CG  ARG  23     46.325  54.321  -2.904  1.00 17.51      A1
ATOM  133 CD  ARG  23     45.095  54.446  -3.769  1.00 21.54      A1
ATOM  134 NE  ARG  23     45.076  53.437  -4.809  1.00 24.82      A1
ATOM  135 HE  ARG  23     45.642  52.647  -4.701  1.00  0.00      A1
ATOM  136 CZ  ARG  23     44.323  53.556  -5.904  1.00 27.69      A1
ATOM  137 NH1 ARG  23     43.567  54.669  -6.006  1.00 29.51      A1
ATOM  138 HH11 ARG  23    43.562  55.377  -5.303  1.00  0.00      A1
ATOM  139 HH12 ARG  23    42.956  54.730  -6.789  1.00  0.00      A1
ATOM  140 NH2 ARG  23     44.345  52.604  -6.891  1.00 24.22      A1
ATOM  141 HH21 ARG  23    43.780  52.713  -7.709  1.00  0.00      A1
ATOM  142 HH22 ARG  23    44.936  51.802  -6.793  1.00  0.00      A1
ATOM  143 C   ARG  23     45.458  57.285  -0.560  1.00 20.56      A1
ATOM  144 O   ARG  23     44.374  57.254   0.042  1.00 20.04      A1
ATOM  145 N   LYS  24     46.485  58.015  -0.118  1.00 22.67      A1
ATOM  146 H   LYS  24     47.291  58.105  -0.668  1.00  0.00      A1
ATOM  147 CA  LYS  24     46.431  58.729   1.166  1.00 22.85      A1
ATOM  148 CB  LYS  24     47.811  59.255   1.506  1.00 26.86      A1
ATOM  149 CG  LYS  24     47.821  59.661   2.971  1.00 33.79      A1
ATOM  150 CD  LYS  24     49.121  60.265   3.404  1.00 40.73      A1
ATOM  151 CE  LYS  24     50.258  59.258   3.335  1.00 46.19      A1
ATOM  152 NZ  LYS  24     51.532  59.975   3.333  1.00 51.19      A1
ATOM  153 HZ1 LYS  24     51.637  60.498   4.225  1.00  0.00      A1
ATOM  154 HZ2 LYS  24     51.539  60.651   2.539  1.00  0.00      A1
ATOM  155 HZ3 LYS  24     52.317  59.303   3.216  1.00  0.00      A1
ATOM  156 C   LYS  24     45.455  59.893   1.101  1.00 21.66      A1
ATOM  157 O   LYS  24     44.588  60.068   1.962  1.00 20.80      A1
ATOM  158 N   ILE  25     45.549  60.696   0.044  1.00 21.66      A1
ATOM  159 H   ILE  25     46.242  60.509  -0.629  1.00  0.00      A1
ATOM  160 CA  ILE  25     44.667  61.841  -0.115  1.00 22.53      A1
ATOM  161 CB  ILE  25     45.075  62.694  -1.307  1.00 22.15      A1
ATOM  162 CG2 ILE  25     44.097  63.834  -1.439  1.00 20.44      A1
ATOM  163 CG1 ILE  25     46.475  63.230  -1.136  1.00 21.03      A1
ATOM  164 CD  ILE  25     47.188  63.281  -2.497  1.00 20.04      A1
ATOM  165 C   ILE  25     43.263  61.308  -0.352  1.00 21.75      A1
ATOM  166 O   ILE  25     42.339  61.839   0.301  1.00 26.13      A1
ATOM  167 N   GLN  26     43.065  60.289  -1.244  1.00 22.79      A1
ATOM  168 H   GLN  26     43.842  59.926  -1.726  1.00  0.00      A1
ATOM  169 CA  GLN  26     41.737  59.713  -1.437  1.00 20.12      A1
ATOM  170 CB  GLN  26     41.729  58.539  -2.341  1.00 18.89      A1
ATOM  171 CG  GLN  26     42.203  59.042  -3.627  1.00 19.77      A1
ATOM  172 CD  GLN  26     42.163  57.996  -4.684  1.00 24.26      A1
ATOM  173 OE1 GLN  26     42.550  56.853  -4.465  1.00 25.82      A1
ATOM  174 NE2 GLN  26     41.732  58.351  -5.890  1.00 27.68      A1
ATOM  175 HE21 GLN  26    41.421  59.265  -6.042  1.00  0.00      A1
ATOM  176 HE22 GLN  26    41.743  57.649  -6.552  1.00  0.00      A1
ATOM  177 C   GLN  26     41.207  59.239  -0.111  1.00 21.88      A1
ATOM  178 O   GLN  26     40.067  59.550   0.220  1.00 27.02      A1
ATOM  179 N   GLY  27     41.952  58.622   0.773  1.00 22.54      A1
ATOM  180 H   GLY  27     42.891  58.420   0.576  1.00  0.00      A1
ATOM  181 CA  GLY  27     41.386  58.191   2.037  1.00 25.55      A1
ATOM  182 C   GLY  27     40.936  59.352   2.890  1.00 27.80      A1
ATOM  183 O   GLY  27     39.889  59.251   3.526  1.00 29.95      A1
ATOM  184 N   ASP  28     41.683  60.460   2.915  1.00 29.39      A1
ATOM  185 H   ASP  28     42.547  60.454   2.448  1.00  0.00      A1
ATOM  186 CA  ASP  28     41.257  61.680   3.624  1.00 28.45      A1
ATOM  187 CB  ASP  28     42.266  62.789   3.552  1.00 30.13      A1
ATOM  188 CG  ASP  28     43.737  62.502   3.777  1.00 31.72      A1
ATOM  189 OD1 ASP  28     44.539  63.024   2.995  1.00 31.95      A1
ATOM  190 OD2 ASP  28     44.063  61.811   4.741  1.00 32.00      A1
ATOM  191 C   ASP  28     39.994  62.264   2.960  1.00 25.81      A1
ATOM  192 O   ASP  28     39.101  62.699   3.655  1.00 26.21      A1
ATOM  193 N   GLY  29     39.882  62.270   1.631  1.00 23.93      A1
ATOM  194 H   GLY  29     40.660  61.950   1.135  1.00  0.00      A1
ATOM  195 CA  GLY  29     38.729  62.694   0.886  1.00 25.69      A1
ATOM  196 C   GLY  29     37.528  61.961   1.418  1.00 22.36      A1
ATOM  197 O   GLY  29     36.648  62.558   2.061  1.00 28.14      A1
ATOM  198 N   ALA  30     37.646  60.628   1.295  1.00 27.85      A1
ATOM  199 H   ALA  30     38.442  60.288   0.843  1.00  0.00      A1
ATOM  200 CA  ALA  30     36.683  59.655   1.814  1.00 25.94      A1
ATOM  201 CB  ALA  30     37.269  58.303   1.556  1.00 22.15      A1
ATOM  202 C   ALA  30     36.356  59.842   3.308  1.00 27.18      A1
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FIGURE 5

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ATOM  203 O   ALA  30    35.194 59.772  3.754 1.00 28.82    A1
ATOM  204 N   ALA  31    37.340 60.105  4.150 1.00 27.16    A1
ATOM  205 H   ALA  31    38.253 60.114  3.809 1.00  0.00    A1
ATOM  206 CA  ALA  31    37.113 60.470  5.531 1.00 27.70    A1
ATOM  207 CB  ALA  31    38.383 60.881  6.177 1.00 27.65    A1
ATOM  208 C   ALA  31    36.178 61.675  5.660 1.00 30.01    A1
ATOM  209 O   ALA  31    35.195 61.624  6.413 1.00 32.91    A1
ATOM  210 N   LEU  32    36.397 62.744  4.895 1.00 27.63    A1
ATOM  211 H   LEU  32    37.133 62.734  4.242 1.00  0.00    A1
ATOM  212 CA  LEU  32    35.560 63.898  4.997 1.00 28.52    A1
ATOM  213 CB  LEU  32    36.226 65.019  4.167 1.00 32.94    A1
ATOM  214 CG  LEU  32    35.658 66.472  4.091 1.00 32.54    A1
ATOM  215 CD1 LEU  32    35.516 67.082  5.499 1.00 32.87    A1
ATOM  216 CD2 LEU  32    36.555 67.267  3.181 1.00 30.97    A1
ATOM  217 C   LEU  32    34.133 63.597  4.518 1.00 27.87    A1
ATOM  218 O   LEU  32    33.169 63.889  5.250 1.00 25.93    A1
ATOM  219 N   GLN  33    33.977 63.028  3.315 1.00 27.51    A1
ATOM  220 H   GLN  33    34.787 62.826  2.802 1.00  0.00    A1
ATOM  221 CA  GLN  33    32.687 62.671  2.775 1.00 30.40    A1
ATOM  222 CB  GLN  33    32.737 61.721  1.614 1.00 29.47    A1
ATOM  223 CG  GLN  33    32.888 62.584  0.436 1.00 29.26    A1
ATOM  224 CD  GLN  33    33.015 61.869 -0.887 1.00 30.21    A1
ATOM  225 OE1 GLN  33    34.064 61.495 -1.452 1.00 29.61    A1
ATOM  226 NE2 GLN  33    31.823 61.759 -1.426 1.00 33.19    A1
ATOM  227 HE21 GLN 33    31.781 61.328 -2.302 1.00  0.00    A1
ATOM  228 HE22 GLN 33    31.042 62.060 -0.914 1.00  0.00    A1
ATOM  229 C   GLN  33    31.839 61.963  3.788 1.00 35.60    A1
ATOM  230 O   GLN  33    30.715 62.416  4.073 1.00 36.49    A1
ATOM  231 N   GLU  34    32.386 60.925  4.438 1.00 39.81    A1
ATOM  232 H   GLU  34    33.340 60.707  4.328 1.00  0.00    A1
ATOM  233 CA  GLU  34    31.541 60.131  5.304 1.00 43.24    A1
ATOM  234 CB  GLU  34    32.228 58.792  5.571 1.00 46.46    A1
ATOM  235 CG  GLU  34    33.274 58.721  6.624 1.00 55.01    A1
ATOM  236 CD  GLU  34    32.777 58.092  7.930 1.00 60.29    A1
ATOM  237 OE1 GLU  34    33.483 57.186  8.412 1.00 63.26    A1
ATOM  238 OE2 GLU  34    31.724 58.504  8.459 1.00 60.44    A1
ATOM  239 C   GLU  34    31.218 60.877  6.564 1.00 43.59    A1
ATOM  240 O   GLU  34    30.175 60.631  7.161 1.00 44.87    A1
ATOM  241 N   LYS  35    32.045 61.811  6.998 1.00 44.80    A1
ATOM  242 H   LYS  35    32.923 61.931  6.569 1.00  0.00    A1
ATOM  243 CA  LYS  35    31.674 62.634  8.134 1.00 45.43    A1
ATOM  244 CB  LYS  35    32.881 63.364  8.686 1.00 47.67    A1
ATOM  245 CG  LYS  35    33.701 62.414  9.510 1.00 52.75    A1
ATOM  246 CD  LYS  35    35.084 63.021  9.548 1.00 57.55    A1
ATOM  247 CE  LYS  35    36.067 62.099 10.238 1.00 60.35    A1
ATOM  248 NZ  LYS  35    35.810 62.064 11.669 1.00 62.91    A1
ATOM  249 HZ1 LYS  35    34.838 61.733 11.840 1.00  0.00    A1
ATOM  250 HZ2 LYS  35    35.930 63.011 12.078 1.00  0.00    A1
ATOM  251 HZ3 LYS  35    36.477 61.405 12.119 1.00  0.00    A1
ATOM  252 C   LYS  35    30.630 63.660  7.697 1.00 44.45    A1
ATOM  253 O   LYS  35    29.730 63.999  8.478 1.00 44.61    A1
ATOM  254 N   LEU  36    30.652 64.190  6.480 1.00 41.21    A1
ATOM  255 H   LEU  36    31.343 63.930  5.836 1.00  0.00    A1
ATOM  256 CA  LEU  36    29.647 65.157  6.144 1.00 40.25    A1
ATOM  257 CB  LEU  36    30.070 65.899  4.889 1.00 39.03    A1
ATOM  258 CG  LEU  36    31.253 66.834  4.935 1.00 33.99    A1
ATOM  259 CD1 LEU  36    31.438 67.404  3.571 1.00 42.08    A1
ATOM  260 CD2 LEU  36    31.034 67.939  5.928 1.00 35.05    A1
ATOM  261 C   LEU  36    28.332 64.414  5.941 1.00 41.90    A1
ATOM  262 O   LEU  36    27.267 64.828  6.431 1.00 42.30    A1
ATOM  263 N   CYS  37    28.392 63.251  5.309 1.00 42.64    A1
ATOM  264 H   CYS  37    29.250 62.904  5.020 1.00  0.00    A1
ATOM  265 CA  CYS  37    27.216 62.469  5.084 1.00 43.54    A1
ATOM  266 C   CYS  37    26.638 62.026  6.362 1.00 44.65    A1
ATOM  267 O   CYS  37    25.426 61.997  6.459 1.00 46.40    A1
ATOM  268 CB  CYS  37    27.474 61.240  4.313 1.00 44.60    A1
ATOM  269 SG  CYS  37    26.133 60.038  4.530 1.00 43.86    A1
ATOM  270 N   ALA  38    27.465 61.734  7.342 1.00 45.96    A1
ATOM  271 H   ALA  38    28.433 61.707  7.202 1.00  0.00    A1
ATOM  272 CA  ALA  38    26.932 61.261  8.592 1.00 48.03    A1
ATOM  273 CB  ALA  38    27.869 60.140  9.108 1.00 48.64    A1
ATOM  274 C   ALA  38    26.748 62.358  9.624 1.00 48.89    A1
ATOM  275 O   ALA  38    26.103 62.085 10.621 1.00 50.72    A1
ATOM  276 N   THR  39    27.256 63.590  9.512 1.00 50.66    A1
ATOM  277 H   THR  39    27.858 63.780  8.770 1.00  0.00    A1
ATOM  278 CA  THR  39    26.976 64.638 10.503 1.00 51.54    A1
ATOM  279 CB  THR  39    28.179 65.593 10.690 1.00 51.76    A1
ATOM  280 OG1 THR  39    29.294 64.826 11.126 1.00 52.65    A1
ATOM  281 HG1 THR  39    29.749 64.481 10.355 1.00  0.00    A1
ATOM  282 CG2 THR  39    27.900 66.655 11.729 1.00 51.62    A1
ATOM  283 C   THR  39    25.775 65.466 10.037 1.00 52.17    A1
ATOM  284 O   THR  39    24.886 65.882 10.781 1.00 52.15    A1
ATOM  285 N   TYR  40    25.751 65.720  8.738 1.00 52.83    A1
ATOM  286 H   TYR  40    26.420 65.331  8.139 1.00  0.00    A1
ATOM  287 CA  TYR  40    24.729 66.561  8.165 1.00 52.53    A1
ATOM  288 CB  TYR  40    25.314 67.872  7.696 1.00 52.15    A1
ATOM  289 CG  TYR  40    26.399 68.458  8.552 1.00 54.11    A1
ATOM  290 CD1 TYR  40    27.678 68.341  8.062 1.00 56.50    A1
ATOM  291 CE1 TYR  40    28.719 68.934  8.724 1.00 58.28    A1
ATOM  292 CD2 TYR  40    26.122 69.144  9.714 1.00 54.86    A1
ATOM  293 CE2 TYR  40    27.170 69.746 10.378 1.00 56.20    A1
ATOM  294 CZ  TYR  40    28.453 69.642  9.872 1.00 58.26    A1
ATOM  295 OH  TYR  40    29.513 70.310 10.463 1.00 61.00    A1
ATOM  296 HH  TYR  40    30.179 70.443  9.782 1.00  0.00    A1
ATOM  297 C   TYR  40    24.035 65.911  6.981 1.00 51.75    A1
ATOM  298 O   TYR  40    23.662 66.578  6.024 1.00 52.52    A1
ATOM  299 N   LYS  41    23.941 64.600  6.965 1.00 50.54    A1
ATOM  300 H   LYS  41    24.474 64.064  7.583 1.00  0.00    A1
ATOM  301 CA  LYS  41    23.112 63.885  6.029 1.00 50.48    A1
ATOM  302 CB  LYS  41    21.641 63.989  6.540 1.00 50.62    A1
ATOM  303 CG  LYS  41    21.387 63.326  7.911 1.00 52.11    A1
ATOM  304 CD  LYS  41    20.112 63.878  8.574 1.00 55.54    A1
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FIGURE 5

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ATOM  305 CE  LYS  41     19.578  63.087   9.820  1.00 58.79      A1
ATOM  306 NZ  LYS  41     18.374  63.648  10.457  1.00 58.31      A1
ATOM  307 HZ1 LYS  41     17.605  63.688   9.757  1.00  0.00      A1
ATOM  308 HZ2 LYS  41     18.578  64.607  10.803  1.00  0.00      A1
ATOM  309 HZ3 LYS  41     18.084  63.043  11.252  1.00  0.00      A1
ATOM  310 C   LYS  41     23.251  64.318   4.588  1.00 49.92      A1
ATOM  311 O   LYS  41     22.312  64.124   3.793  1.00 51.49      A1
ATOM  312 N   LEU  42     24.432  64.893   4.246  1.00 48.28      A1
ATOM  313 H   LEU  42     25.103  65.050   4.937  1.00  0.00      A1
ATOM  314 CA  LEU  42     24.742  65.286   2.859  1.00 46.61      A1
ATOM  315 CB  LEU  42     25.565  66.574   2.757  1.00 44.69      A1
ATOM  316 CG  LEU  42     24.807  67.802   3.218  1.00 42.63      A1
ATOM  317 CD1 LEU  42     25.718  68.580   4.097  1.00 43.29      A1
ATOM  318 CD2 LEU  42     24.283  68.590   2.045  1.00 41.26      A1
ATOM  319 C   LEU  42     25.580  64.124   2.397  1.00 45.46      A1
ATOM  320 O   LEU  42     26.766  64.017   2.711  1.00 46.32      A1
ATOM  321 N   CYS  43     24.882  63.193   1.754  1.00 44.09      A1
ATOM  322 H   CYS  43     23.925  63.353   1.619  1.00  0.00      A1
ATOM  323 CA  CYS  43     25.480  61.951   1.358  1.00 42.87      A1
ATOM  324 C   CYS  43     25.448  61.846  -0.123  1.00 41.62      A1
ATOM  325 O   CYS  43     25.762  60.805  -0.666  1.00 41.99      A1
ATOM  326 CB  CYS  43     24.716  60.796   2.026  1.00 41.77      A1
ATOM  327 SG  CYS  43     24.523  61.011   3.835  1.00 45.91      A1
ATOM  328 N   HIS  44     25.057  62.846  -0.882  1.00 42.90      A1
ATOM  329 H   HIS  44     24.841  63.721  -0.491  1.00  0.00      A1
ATOM  330 CA  HIS  44     25.069  62.680  -2.320  1.00 44.60      A1
ATOM  331 CB  HIS  44     23.653  62.264  -2.825  1.00 48.40      A1
ATOM  332 CG  HIS  44     23.085  60.935  -2.310  1.00 50.37      A1
ATOM  333 CD2 HIS  44     22.178  60.844  -1.272  1.00 50.52      A1
ATOM  334 ND1 HIS  44     23.358  59.689  -2.713  1.00 52.28      A1
ATOM  335 HD1 HIS  44     24.130  59.394  -3.251  1.00  0.00      A1
ATOM  336 CE1 HIS  44     22.652  58.873  -1.955  1.00 51.92      A1
ATOM  337 NE2 HIS  44     21.947  59.565  -1.091  1.00 50.53      A1
ATOM  338 HE2 HIS  44     21.290  59.189  -0.466  1.00  0.00      A1
ATOM  339 C   HIS  44     25.522  63.941  -3.047  1.00 43.69      A1
ATOM  340 O   HIS  44     24.765  64.906  -3.108  1.00 43.00      A1
ATOM  341 N   PRO  45     26.710  63.978  -3.667  1.00 43.07      A1
ATOM  342 CD  PRO  45     27.785  62.995  -3.501  1.00 42.17      A1
ATOM  343 CA  PRO  45     27.133  65.024  -4.570  1.00 42.50      A1
ATOM  344 CB  PRO  45     28.380  64.466  -5.217  1.00 39.76      A1
ATOM  345 CG  PRO  45     28.995  63.680  -4.123  1.00 39.09      A1
ATOM  346 C   PRO  45     26.071  65.423  -5.585  1.00 44.49      A1
ATOM  347 O   PRO  45     25.876  66.612  -5.801  1.00 45.36      A1
ATOM  348 N   GLU  46     25.334  64.501  -6.225  1.00 45.36      A1
ATOM  349 H   GLU  46     25.464  63.561  -5.996  1.00  0.00      A1
ATOM  350 CA  GLU  46     24.406  64.806  -7.319  1.00 45.46      A1
ATOM  351 CB  GLU  46     23.952  63.515  -7.997  1.00 50.54      A1
ATOM  352 CG  GLU  46     24.462  63.460  -9.445  1.00 58.48      A1
ATOM  353 CD  GLU  46     23.637  64.215 -10.502  1.00 64.93      A1
ATOM  354 OE1 GLU  46     23.642  65.455 -10.516  1.00 68.55      A1
ATOM  355 OE2 GLU  46     22.995  63.554 -11.332  1.00 68.31      A1
ATOM  356 C   GLU  46     23.181  65.584  -6.937  1.00 42.96      A1
ATOM  357 O   GLU  46     22.532  66.223  -7.748  1.00 41.71      A1
ATOM  358 N   GLU  47     22.919  65.563  -5.654  1.00 41.96      A1
ATOM  359 H   GLU  47     23.507  65.098  -5.028  1.00  0.00      A1
ATOM  360 CA  GLU  47     21.818  66.301  -5.144  1.00 43.21      A1
ATOM  361 CB  GLU  47     21.294  65.487  -3.963  1.00 43.24      A1
ATOM  362 CG  GLU  47     21.409  65.925  -2.515  1.00 46.07      A1
ATOM  363 CD  GLU  47     20.812  64.907  -1.547  1.00 47.86      A1
ATOM  364 OE1 GLU  47     19.847  64.225  -1.910  1.00 50.99      A1
ATOM  365 OE2 GLU  47     21.313  64.780  -0.427  1.00 49.47      A1
ATOM  366 C   GLU  47     22.295  67.718  -4.809  1.00 44.04      A1
ATOM  367 O   GLU  47     21.532  68.547  -4.292  1.00 44.60      A1
ATOM  368 N   LEU  48     23.567  68.015  -5.121  1.00 43.05      A1
ATOM  369 H   LEU  48     24.140  67.310  -5.465  1.00  0.00      A1
ATOM  370 CA  LEU  48     24.166  69.318  -4.904  1.00 42.42      A1
ATOM  371 CB  LEU  48     25.223  69.201  -3.858  1.00 40.55      A1
ATOM  372 CG  LEU  48     24.920  68.695  -2.489  1.00 41.87      A1
ATOM  373 CD1 LEU  48     26.277  68.424  -1.892  1.00 41.71      A1
ATOM  374 CD2 LEU  48     24.096  69.670  -1.633  1.00 41.13      A1
ATOM  375 C   LEU  48     24.792  69.937  -6.166  1.00 42.37      A1
ATOM  376 O   LEU  48     25.439  70.994  -6.098  1.00 42.37      A1
ATOM  377 N   VAL  49     24.566  69.366  -7.347  1.00 41.52      A1
ATOM  378 H   VAL  49     23.951  68.602  -7.362  1.00  0.00      A1
ATOM  379 CA  VAL  49     25.191  69.822  -8.578  1.00 43.34      A1
ATOM  380 CB  VAL  49     24.890  68.761  -9.636  1.00 44.29      A1
ATOM  381 CG1 VAL  49     23.381  68.709  -9.830  1.00 47.50      A1
ATOM  382 CG2 VAL  49     25.540  69.086 -10.975  1.00 45.25      A1
ATOM  383 C   VAL  49     24.740  71.214  -9.028  1.00 44.98      A1
ATOM  384 O   VAL  49     25.401  71.901  -9.814  1.00 46.03      A1
ATOM  385 N   LEU  50     23.565  71.602  -8.530  1.00 46.16      A1
ATOM  386 H   LEU  50     23.081  70.933  -8.006  1.00  0.00      A1
ATOM  387 CA  LEU  50     22.908  72.895  -8.729  1.00 46.03      A1
ATOM  388 CB  LEU  50     21.469  72.769  -8.264  1.00 46.43      A1
ATOM  389 CG  LEU  50     20.443  73.718  -8.760  1.00 44.16      A1
ATOM  390 CD1 LEU  50     20.259  73.558 -10.243  1.00 44.79      A1
ATOM  391 CD2 LEU  50     19.159  73.400  -8.079  1.00 44.66      A1
ATOM  392 C   LEU  50     23.632  73.968  -7.917  1.00 45.85      A1
ATOM  393 O   LEU  50     23.996  74.989  -8.484  1.00 44.52      A1
ATOM  394 N   LEU  51     23.853  73.764  -6.606  1.00 45.44      A1
ATOM  395 H   LEU  51     23.489  72.958  -6.189  1.00  0.00      A1
ATOM  396 CA  LEU  51     24.676  74.656  -5.805  1.00 46.04      A1
ATOM  397 CB  LEU  51     24.860  74.084  -4.435  1.00 45.53      A1
ATOM  398 CG  LEU  51     25.741  74.931  -3.535  1.00 47.78      A1
ATOM  399 CD1 LEU  51     25.148  76.320  -3.322  1.00 47.13      A1
ATOM  400 CD2 LEU  51     25.902  74.202  -2.219  1.00 48.33      A1
ATOM  401 C   LEU  51     26.064  74.845  -6.436  1.00 46.27      A1
ATOM  402 O   LEU  51     26.551  75.966  -6.612  1.00 47.62      A1
ATOM  403 N   GLY  52     26.702  73.736  -6.809  1.00 44.84      A1
ATOM  404 H   GLY  52     26.306  72.869  -6.578  1.00  0.00      A1
ATOM  405 CA  GLY  52     27.989  73.758  -7.453  1.00 42.91      A1
ATOM  406 C   GLY  52     27.984  74.533  -8.750  1.00 42.47      A1
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EP 0 612 846 A1

FIGURE 5

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ATOM  407 O   GLY  52     28.853  75.364  -8.983  1.00 42.06      A1
ATOM  408 N   HIS  53     27.047  74.307  -9.653  1.00 42.02      A1
ATOM  409 H   HIS  53     26.366  73.624  -9.471  1.00  0.00      A1
ATOM  410 CA  HIS  53     27.009  75.104 -10.861  1.00 42.23      A1
ATOM  411 CB  HIS  53     25.842  74.689 -11.706  1.00 42.21      A1
ATOM  412 CG  HIS  53     26.076  73.399 -12.460  1.00 44.60      A1
ATOM  413 CD2 HIS  53     25.112  72.774 -13.200  1.00 47.49      A1
ATOM  414 ND1 HIS  53     27.180  72.669 -12.578  1.00 46.76      A1
ATOM  415 HD1 HIS  53     28.039  72.853 -12.139  1.00  0.00      A1
ATOM  416 CE1 HIS  53     26.954  71.641 -13.346  1.00 46.90      A1
ATOM  417 NE2 HIS  53     25.704  71.725 -13.707  1.00 50.22      A1
ATOM  418 HE2 HIS  53     25.237  71.033 -14.239  1.00  0.00      A1
ATOM  419 C   HIS  53     26.893  76.585 -10.536  1.00 42.72      A1
ATOM  420 O   HIS  53     27.622  77.399 -11.068  1.00 42.03      A1
ATOM  421 N   SER  54     26.099  76.920  -9.535  1.00 45.08      A1
ATOM  422 H   SER  54     25.673  76.218  -9.001  1.00  0.00      A1
ATOM  423 CA  SER  54     25.792  78.278  -9.177  1.00 46.92      A1
ATOM  424 CB  SER  54     24.576  78.181  -8.289  1.00 48.86      A1
ATOM  425 OG  SER  54     23.521  77.616  -9.112  1.00 53.06      A1
ATOM  426 HG  SER  54     23.465  76.677  -8.918  1.00  0.00      A1
ATOM  427 C   SER  54     26.939  79.033  -8.549  1.00 47.92      A1
ATOM  428 O   SER  54     27.038  80.264  -8.655  1.00 49.60      A1
ATOM  429 N   LEU  55     27.837  78.273  -7.933  1.00 47.59      A1
ATOM  430 H   LEU  55     27.638  77.322  -7.791  1.00  0.00      A1
ATOM  431 CA  LEU  55     29.075  78.810  -7.401  1.00 45.27      A1
ATOM  432 CB  LEU  55     29.552  77.913  -6.243  1.00 45.49      A1
ATOM  433 CG  LEU  55     28.840  77.992  -4.874  1.00 47.30      A1
ATOM  434 CD1 LEU  55     28.876  76.596  -4.299  1.00 49.52      A1
ATOM  435 CD2 LEU  55     29.530  78.921  -3.862  1.00 45.69      A1
ATOM  436 C   LEU  55     30.133  78.889  -8.492  1.00 43.63      A1
ATOM  437 O   LEU  55     31.247  79.350  -8.272  1.00 43.24      A1
ATOM  438 N   GLY  56     29.855  78.383  -9.675  1.00 43.55      A1
ATOM  439 H   GLY  56     28.984  77.975  -9.828  1.00  0.00      A1
ATOM  440 CA  GLY  56     30.814  78.390 -10.753  1.00 45.59      A1
ATOM  441 C   GLY  56     32.182  77.811 -10.392  1.00 46.76      A1
ATOM  442 O   GLY  56     33.171  78.213 -11.015  1.00 47.31      A1
ATOM  443 N   ILE  57     32.247  76.885  -9.412  1.00 47.49      A1
ATOM  444 H   ILE  57     31.392  76.594  -9.042  1.00  0.00      A1
ATOM  445 CA  ILE  57     33.486  76.249  -8.950  1.00 48.28      A1
ATOM  446 CB  ILE  57     33.144  75.172  -7.863  1.00 47.79      A1
ATOM  447 CG2 ILE  57     34.457  74.591  -7.348  1.00 46.85      A1
ATOM  448 CG1 ILE  57     32.338  75.764  -6.701  1.00 45.09      A1
ATOM  449 CD  ILE  57     31.859  74.739  -5.659  1.00 41.23      A1
ATOM  450 C   ILE  57     34.276  75.602 -10.115  1.00 49.15      A1
ATOM  451 O   ILE  57     33.678  74.935 -10.968  1.00 49.04      A1
ATOM  452 N   PRO  58     35.596  75.817 -10.248  1.00 49.75      A1
ATOM  453 CD  PRO  58     36.402  76.743  -9.433  1.00 50.94      A1
ATOM  454 CA  PRO  58     36.421  75.228 -11.302  1.00 50.72      A1
ATOM  455 CB  PRO  58     37.525  76.241 -11.488  1.00 50.92      A1
ATOM  456 CG  PRO  58     37.814  76.663 -10.041  1.00 50.82      A1
ATOM  457 C   PRO  58     36.916  73.845 -10.875  1.00 50.36      A1
ATOM  458 O   PRO  58     37.187  73.599  -9.691  1.00 49.75      A1
ATOM  459 N   TRP  59     37.030  72.927 -11.816  1.00 50.37      A1
ATOM  460 H   TRP  59     36.888  73.141 -12.760  1.00  0.00      A1
ATOM  461 CA  TRP  59     37.524  71.595 -11.482  1.00 51.78      A1
ATOM  462 CB  TRP  59     36.435  70.562 -11.857  1.00 49.06      A1
ATOM  463 CG  TRP  59     35.254  70.712 -10.889  1.00 46.87      A1
ATOM  464 CD2 TRP  59     35.320  70.845  -9.521  1.00 44.06      A1
ATOM  465 CE2 TRP  59     33.998  71.027  -9.205  1.00 44.18      A1
ATOM  466 CE3 TRP  59     36.274  70.842  -8.538  1.00 44.03      A1
ATOM  467 CD1 TRP  59     33.972  70.794 -11.354  1.00 45.17      A1
ATOM  468 NE1 TRP  59     33.229  70.994 -10.297  1.00 44.17      A1
ATOM  469 HE1 TRP  59     32.301  71.312 -10.332  1.00  0.00      A1
ATOM  470 CZ2 TRP  59     33.598  71.215  -7.916  1.00 45.60      A1
ATOM  471 CZ3 TRP  59     35.893  71.028  -7.243  1.00 45.25      A1
ATOM  472 CH2 TRP  59     34.565  71.214  -6.938  1.00 46.43      A1
ATOM  473 C   TRP  59     38.815  71.435 -12.256  1.00 52.84      A1
ATOM  474 O   TRP  59     38.842  71.972 -13.372  1.00 54.96      A1
ATOM  475 N   ALA  60     39.912  70.834 -11.777  1.00 51.97      A1
ATOM  476 H   ALA  60     39.857  70.269 -10.977  1.00  0.00      A1
ATOM  477 CA  ALA  60     41.108  70.870 -12.609  1.00 52.18      A1
ATOM  478 CB  ALA  60     42.303  70.610 -11.748  1.00 51.75      A1
ATOM  479 C   ALA  60     41.055  69.857 -13.746  1.00 52.16      A1
ATOM  480 O   ALA  60     40.545  68.760 -13.530  1.00 52.17      A1
ATOM  481 N   PRO  61     41.435  70.145 -14.986  1.00 54.34      A1
ATOM  482 CD  PRO  61     41.370  71.458 -15.622  1.00 54.76      A1
ATOM  483 CA  PRO  61     41.691  69.145 -15.993  1.00 55.57      A1
ATOM  484 CB  PRO  61     41.792  69.918 -17.310  1.00 54.95      A1
ATOM  485 CG  PRO  61     42.211  71.297 -16.901  1.00 54.05      A1
ATOM  486 C   PRO  61     42.934  68.333 -15.690  1.00 57.54      A1
ATOM  487 O   PRO  61     43.757  68.661 -14.834  1.00 57.20      A1
ATOM  488 N   LEU  62     43.040  67.271 -16.486  1.00 59.98      A1
ATOM  489 H   LEU  62     42.285  67.067 -17.077  1.00  0.00      A1
ATOM  490 CA  LEU  62     44.184  66.370 -16.471  1.00 63.64      A1
ATOM  491 CB  LEU  62     44.062  65.417 -15.260  1.00 63.72      A1
ATOM  492 CG  LEU  62     45.323  64.691 -14.865  1.00 64.43      A1
ATOM  493 CD1 LEU  62     46.394  65.704 -14.488  1.00 64.02      A1
ATOM  494 CD2 LEU  62     45.016  63.764 -13.717  1.00 64.98      A1
ATOM  495 C   LEU  62     44.214  65.611 -17.812  1.00 65.69      A1
ATOM  496 OT1 LEU  62     44.256  66.302 -18.844  1.00 68.47      A1
ATOM  497 OT2 LEU  62     44.194  64.371 -17.845  1.00 66.57      A1
ATOM  498 CB  LEU  72     57.448  63.159 -19.422  1.00 63.44      A2
ATOM  499 CG  LEU  72     57.716  62.495 -18.117  1.00 63.40      A2
ATOM  500 CD1 LEU  72     56.719  61.408 -17.913  1.00 61.50      A2
ATOM  501 CD2 LEU  72     59.107  61.901 -18.121  1.00 63.22      A2
ATOM  502 C   LEU  72     55.897  65.084 -18.876  1.00 65.40      A2
ATOM  503 O   LEU  72     54.827  65.301 -18.316  1.00 67.30      A2
ATOM  504 HT1 LEU  72     56.469  64.683 -21.261  1.00  0.00      A2
ATOM  505 HT2 LEU  72     54.827  64.355 -20.951  1.00  0.00      A2
ATOM  506 N   LEU  72     55.795  63.983 -20.899  1.00 66.29      A2
ATOM  507 HT3 LEU  72     55.866  63.098 -21.449  1.00  0.00      A2
ATOM  508 CA  LEU  72     56.064  63.714 -19.512  1.00 64.91      A2
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FIGURE 5

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ATOM  509 N   ALA  73    56.807  66.046 -19.086  1.00 64.54      A2
ATOM  510 H   ALA  73    57.690  65.804 -19.432  1.00  0.00      A2
ATOM  511 CA  ALA  73    56.707  67.433 -18.615  1.00 62.55      A2
ATOM  512 CB  ALA  73    57.553  68.314 -19.529  1.00 64.84      A2
ATOM  513 C   ALA  73    55.319  68.024 -18.539  1.00 60.37      A2
ATOM  514 O   ALA  73    54.801  68.180 -17.456  1.00 59.42      A2
ATOM  515 N   GLY  74    54.693  68.226 -19.691  1.00 59.72      A2
ATOM  516 H   GLY  74    55.212  68.174 -20.514  1.00  0.00      A2
ATOM  517 CA  GLY  74    53.336  68.728 -19.816  1.00 59.99      A2
ATOM  518 C   GLY  74    52.327  68.114 -18.865  1.00 60.27      A2
ATOM  519 O   GLY  74    51.880  68.796 -17.935  1.00 60.80      A2
ATOM  520 N   CYS  75    51.945  66.850 -19.030  1.00 59.60      A2
ATOM  521 H   CYS  75    52.160  66.358 -19.839  1.00  0.00      A2
ATOM  522 CA  CYS  75    51.002  66.276 -18.078  1.00 60.17      A2
ATOM  523 CB  CYS  75    50.670  64.801 -18.464  1.00 64.08      A2
ATOM  524 SG  CYS  75    49.832  64.732 -20.096  1.00 73.47      A2
ATOM  525 C   CYS  75    51.502  66.346 -16.642  1.00 56.73      A2
ATOM  526 O   CYS  75    50.734  66.748 -15.765  1.00 55.82      A2
ATOM  527 N   LEU  76    52.795  66.142 -16.396  1.00 53.93      A2
ATOM  528 H   LEU  76    53.423  66.043 -17.137  1.00  0.00      A2
ATOM  529 CA  LEU  76    53.325  66.156 -15.044  1.00 52.94      A2
ATOM  530 CB  LEU  76    54.798  65.754 -15.181  1.00 50.81      A2
ATOM  531 CG  LEU  76    55.575  65.011 -14.090  1.00 49.02      A2
ATOM  532 CD1 LEU  76    54.852  63.740 -13.698  1.00 46.76      A2
ATOM  533 CD2 LEU  76    56.951  64.633 -14.623  1.00 47.67      A2
ATOM  534 C   LEU  76    53.093  67.545 -14.425  1.00 53.65      A2
ATOM  535 O   LEU  76    52.731  67.716 -13.244  1.00 53.50      A2
ATOM  536 N   SER  77    53.137  68.553 -15.301  1.00 53.91      A2
ATOM  537 H   SER  77    53.322  68.361 -16.242  1.00  0.00      A2
ATOM  538 CA  SER  77    52.882  69.932 -14.942  1.00 54.93      A2
ATOM  539 CB  SER  77    53.425  70.835 -16.040  1.00 58.32      A2
ATOM  540 OG  SER  77    54.806  70.587 -16.310  1.00 63.35      A2
ATOM  541 HG  SER  77    54.949  69.637 -16.315  1.00  0.00      A2
ATOM  542 C   SER  77    51.382  70.172 -14.759  1.00 53.47      A2
ATOM  543 O   SER  77    50.982  70.965 -13.899  1.00 53.54      A2
ATOM  544 N   GLN  78    50.509  69.501 -15.512  1.00 51.82      A2
ATOM  545 H   GLN  78    50.857  68.901 -16.207  1.00  0.00      A2
ATOM  546 CA  GLN  78    49.074  69.619 -15.349  1.00 50.74      A2
ATOM  547 CB  GLN  78    48.402  68.877 -16.451  1.00 54.31      A2
ATOM  548 CG  GLN  78    47.420  69.784 -17.160  1.00 58.59      A2
ATOM  549 CD  GLN  78    46.557  68.940 -18.071  1.00 62.32      A2
ATOM  550 OE1 GLN  78    47.005  68.260 -18.998  1.00 65.94      A2
ATOM  551 NE2 GLN  78    45.269  68.889 -17.800  1.00 63.17      A2
ATOM  552 HE21 GLN  78    44.973  69.327 -16.972  1.00  0.00      A2
ATOM  553 HE22 GLN  78    44.704  68.444 -18.456  1.00  0.00      A2
ATOM  554 C   GLN  78    48.591  69.065 -14.011  1.00 48.17      A2
ATOM  555 O   GLN  78    47.691  69.618 -13.368  1.00 46.31      A2
ATOM  556 N   LEU  79    49.236  67.988 -13.564  1.00 45.89      A2
ATOM  557 H   LEU  79    49.920  67.584 -14.140  1.00  0.00      A2
ATOM  558 CA  LEU  79    48.919  67.359 -12.294  1.00 44.54      A2
ATOM  559 CB  LEU  79    49.617  66.015 -12.259  1.00 45.06      A2
ATOM  560 CG  LEU  79    49.154  64.895 -11.351  1.00 45.18      A2
ATOM  561 CD1 LEU  79    49.634  63.594 -11.957  1.00 45.06      A2
ATOM  562 CD2 LEU  79    49.766  64.986 -9.969  1.00 46.03      A2
ATOM  563 C   LEU  79    49.366  68.265 -11.170  1.00 44.49      A2
ATOM  564 O   LEU  79    48.645  68.509 -10.199  1.00 44.20      A2
ATOM  565 N   HIS  80    50.556  68.834 -11.329  1.00 43.83      A2
ATOM  566 H   HIS  80    51.115  68.548 -12.085  1.00  0.00      A2
ATOM  567 CA  HIS  80    51.060  69.788 -10.360  1.00 43.79      A2
ATOM  568 CB  HIS  80    52.456  70.221 -10.810  1.00 44.58      A2
ATOM  569 CG  HIS  80    53.030  71.031 -9.690  1.00 43.75      A2
ATOM  570 CD2 HIS  80    53.484  70.497 -8.517  1.00 47.48      A2
ATOM  571 ND1 HIS  80    53.083  72.343 -9.567  1.00 44.24      A2
ATOM  572 HD1 HIS  80    52.842  73.004 -10.255  1.00  0.00      A2
ATOM  573 CE1 HIS  80    53.530  72.641 -8.376  1.00 44.47      A2
ATOM  574 NE2 HIS  80    53.772  71.520 -7.748  1.00 48.16      A2
ATOM  575 HE2 HIS  80    54.103  71.444 -6.824  1.00  0.00      A2
ATOM  576 C   HIS  80    50.094  70.978 -10.229  1.00 44.40      A2
ATOM  577 O   HIS  80    49.643  71.294 -9.131  1.00 44.28      A2
ATOM  578 N   SER  81    49.733  71.670 -11.309  1.00 45.13      A2
ATOM  579 H   SER  81    50.136  71.459 -12.176  1.00  0.00      A2
ATOM  580 CA  SER  81    48.738  72.742 -11.296  1.00 45.41      A2
ATOM  581 CB  SER  81    48.612  73.347 -12.682  1.00 45.59      A2
ATOM  582 OG  SER  81    49.894  73.444 -13.292  1.00 49.27      A2
ATOM  583 HG  SER  81    50.058  72.670 -13.843  1.00  0.00      A2
ATOM  584 C   SER  81    47.344  72.266 -10.856  1.00 44.85      A2
ATOM  585 O   SER  81    46.604  73.064 -10.256  1.00 46.93      A2
ATOM  586 N   GLY  82    46.946  71.010 -11.092  1.00 42.16      A2
ATOM  587 H   GLY  82    47.513  70.411 -11.614  1.00  0.00      A2
ATOM  588 CA  GLY  82    45.663  70.500 -10.650  1.00 39.39      A2
ATOM  589 C   GLY  82    45.569  70.461 -9.139  1.00 39.30      A2
ATOM  590 O   GLY  82    44.542  70.843 -8.544  1.00 39.64      A2
ATOM  591 N   LEU  83    46.676  70.032 -8.521  1.00 37.57      A2
ATOM  592 H   LEU  83    47.413  69.695 -9.075  1.00  0.00      A2
ATOM  593 CA  LEU  83    46.826  70.007 -7.057  1.00 38.07      A2
ATOM  594 CB  LEU  83    46.133  69.202 -6.748  1.00 35.67      A2
ATOM  595 CG  LEU  83    48.071  67.736 -7.275  1.00 32.51      A2
ATOM  596 CD1 LEU  83    49.442  67.145 -7.319  1.00 29.77      A2
ATOM  597 CD2 LEU  83    47.180  66.973 -6.288  1.00 28.71      A2
ATOM  598 C   LEU  83    46.836  71.386 -6.354  1.00 38.48      A2
ATOM  599 O   LEU  83    46.392  71.627 -5.219  1.00 38.05      A2
ATOM  600 N   PHE  84    47.366  72.338 -7.108  1.00 40.34      A2
ATOM  601 H   PHE  84    47.804  72.078 -7.944  1.00  0.00      A2
ATOM  602 CA  PHE  84    47.414  73.703 -6.688  1.00 41.54      A2
ATOM  603 CB  PHE  84    48.163  74.531 -7.693  1.00 46.88      A2
ATOM  604 CG  PHE  84    48.715  75.777 -6.988  1.00 55.09      A2
ATOM  605 CD1 PHE  84    49.521  75.622 -5.849  1.00 55.44      A2
ATOM  606 CD2 PHE  84    48.396  77.053 -7.469  1.00 55.79      A2
ATOM  607 CE1 PHE  84    50.004  76.737 -5.195  1.00 57.60      A2
ATOM  608 CE2 PHE  84    48.892  78.156 -6.796  1.00 57.25      A2
ATOM  609 CZ  PHE  84    49.688  78.092 -5.667  1.00 58.44      A2
ATOM  610 C   PHE  84    45.994  74.191 -6.591  1.00 40.47      A2
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FIGURE 5

```
ATOM  611 O   PHE  84    45.609 74.749 -5.558 1.00 42.71    A2
ATOM  612 N   LEU  85    45.190 73.953 -7.624 1.00 38.64    A2
ATOM  613 H   LEU  85    45.555 73.527 -8.429 1.00 0.00     A2
ATOM  614 CA  LEU  85    43.794 74.335 -7.584 1.00 38.81    A2
ATOM  615 CB  LEU  85    43.101 73.886 -8.839 1.00 41.27    A2
ATOM  616 CG  LEU  85    41.673 74.403 -9.017 1.00 46.45    A2
ATOM  617 CD1 LEU  85    41.702 75.784 -9.719 1.00 47.80    A2
ATOM  618 CD2 LEU  85    40.860 73.359 -9.787 1.00 48.25    A2
ATOM  619 C   LEU  85    43.079 73.731 -6.386 1.00 38.20    A2
ATOM  620 O   LEU  85    42.498 74.469 -5.582 1.00 38.36    A2
ATOM  621 N   TYR  86    43.150 72.405 -6.198 1.00 37.92    A2
ATOM  622 H   TYR  86    43.637 71.850 -6.845 1.00 0.00     A2
ATOM  623 CA  TYR  86    42.501 71.801 -5.057 1.00 37.15    A2
ATOM  624 CB  TYR  86    42.598 70.255 -5.102 1.00 36.73    A2
ATOM  625 CG  TYR  86    41.561 69.685 -6.081 1.00 33.66    A2
ATOM  626 CD1 TYR  86    41.946 69.312 -7.374 1.00 30.03    A2
ATOM  627 CE1 TYR  86    40.991 68.885 -8.280 1.00 30.08    A2
ATOM  628 CD2 TYR  86    40.224 69.623 -5.666 1.00 32.61    A2
ATOM  629 CE2 TYR  86    39.263 69.203 -6.574 1.00 31.66    A2
ATOM  630 CZ  TYR  86    39.656 68.838 -7.868 1.00 30.57    A2
ATOM  631 OH  TYR  86    38.670 68.428 -8.751 1.00 28.18    A2
ATOM  632 HH  TYR  86    39.107 67.994 -9.485 1.00 0.00     A2
ATOM  633 C   TYR  86    43.054 72.318 -3.746 1.00 37.75    A2
ATOM  634 O   TYR  86    42.173 72.469 -2.889 1.00 39.52    A2
ATOM  635 N   GLN  87    44.347 72.655 -3.478 1.00 36.93    A2
ATOM  636 H   GLN  87    45.044 72.463 -4.140 1.00 0.00     A2
ATOM  637 CA  GLN  87    44.749 73.332 -2.205 1.00 36.40    A2
ATOM  638 CB  GLN  87    46.210 73.668 -2.255 1.00 39.56    A2
ATOM  639 CG  GLN  87    47.126 72.993 -1.237 1.00 46.99    A2
ATOM  640 CD  GLN  87    48.641 73.062 -1.576 1.00 50.96    A2
ATOM  641 OE1 GLN  87    49.144 72.623 -2.627 1.00 52.15    A2
ATOM  642 NE2 GLN  87    49.446 73.608 -0.663 1.00 52.96    A2
ATOM  643 HE21 GLN 87    49.055 73.957  0.164 1.00 0.00     A2
ATOM  644 HE22 GLN 87    50.396 73.621 -0.888 1.00 0.00     A2
ATOM  645 C   GLN  87    43.941 74.652 -2.013 1.00 34.36    A2
ATOM  646 O   GLN  87    43.414 74.990 -0.935 1.00 31.55    A2
ATOM  647 N   GLY  88    43.740 75.335 -3.159 1.00 32.73    A2
ATOM  648 H   GLY  88    44.165 75.005 -3.981 1.00 0.00     A2
ATOM  649 CA  GLY  88    42.948 76.546 -3.232 1.00 30.81    A2
ATOM  650 C   GLY  88    41.540 76.275 -2.731 1.00 30.47    A2
ATOM  651 O   GLY  88    41.130 76.819 -1.703 1.00 30.27    A2
ATOM  652 N   LEU  89    40.802 75.387 -3.406 1.00 29.01    A2
ATOM  653 H   LEU  89    41.220 74.912 -4.154 1.00 0.00     A2
ATOM  654 CA  LEU  89    39.447 75.102 -3.009 1.00 27.60    A2
ATOM  655 CB  LEU  89    38.922 74.073 -3.935 1.00 28.13    A2
ATOM  656 CG  LEU  89    38.764 74.583 -5.340 1.00 29.51    A2
ATOM  657 CD1 LEU  89    38.363 73.530 -6.364 1.00 24.13    A2
ATOM  658 CD2 LEU  89    37.673 75.637 -5.220 1.00 32.87    A2
ATOM  659 C   LEU  89    39.352 74.629 -1.583 1.00 29.88    A2
ATOM  660 O   LEU  89    38.427 75.012 -0.860 1.00 30.81    A2
ATOM  661 N   LEU  90    40.317 73.839 -1.094 1.00 32.59    A2
ATOM  662 H   LEU  90    41.101 73.626 -1.643 1.00 0.00     A2
ATOM  663 CA  LEU  90    40.182 73.274  0.235 1.00 33.41    A2
ATOM  664 CB  LEU  90    41.207 72.234  0.503 1.00 36.15    A2
ATOM  665 CG  LEU  90    41.075 70.971 -0.343 1.00 38.76    A2
ATOM  666 CD1 LEU  90    42.431 70.267 -0.456 1.00 37.21    A2
ATOM  667 CD2 LEU  90    39.995 70.099  0.279 1.00 40.54    A2
ATOM  668 C   LEU  90    40.342 74.319  1.255 1.00 34.21    A2
ATOM  669 O   LEU  90    39.711 74.256  2.313 1.00 35.57    A2
ATOM  670 N   GLN  91    41.188 75.291  0.940 1.00 35.24    A2
ATOM  671 H   GLN  91    41.563 75.264  0.078 1.00 0.00     A2
ATOM  672 CA  GLN  91    41.397 76.373  1.883 1.00 37.60    A2
ATOM  673 CB  GLN  91    42.557 77.182  1.363 1.00 39.65    A2
ATOM  674 CG  GLN  91    43.155 78.237  2.294 1.00 44.37    A2
ATOM  675 CD  GLN  91    44.348 78.799  1.542 1.00 46.96    A2
ATOM  676 OE1 GLN  91    45.235 78.083  1.068 1.00 47.42    A2
ATOM  677 NE2 GLN  91    44.376 80.092  1.341 1.00 46.82    A2
ATOM  678 HE21 GLN 91    43.690 80.685  1.700 1.00 0.00     A2
ATOM  679 HE22 GLN 91    45.108 80.331  0.741 1.00 0.00     A2
ATOM  680 C   GLN  91    40.129 77.231  2.061 1.00 37.22    A2
ATOM  681 O   GLN  91    39.718 77.530  3.186 1.00 36.21    A2
ATOM  682 N   ALA  92    39.456 77.570  0.943 1.00 38.63    A2
ATOM  683 H   ALA  92    39.808 77.205  0.098 1.00 0.00     A2
ATOM  684 CA  ALA  92    38.243 78.402  0.880 1.00 38.10    A2
ATOM  685 CB  ALA  92    37.657 78.436 -0.511 1.00 36.76    A2
ATOM  686 C   ALA  92    37.139 77.905  1.770 1.00 38.95    A2
ATOM  687 O   ALA  92    36.294 78.687  2.194 1.00 42.45    A2
ATOM  688 N   LEU  93    37.151 76.618  2.123 1.00 38.34    A2
ATOM  689 H   LEU  93    37.855 76.040  1.759 1.00 0.00     A2
ATOM  690 CA  LEU  93    36.111 76.018  2.972 1.00 36.90    A2
ATOM  691 CB  LEU  93    36.088 74.463  2.794 1.00 35.24    A2
ATOM  692 CG  LEU  93    35.725 73.992  1.378 1.00 33.55    A2
ATOM  693 CD1 LEU  93    36.159 72.583  1.129 1.00 33.26    A2
ATOM  694 CD2 LEU  93    34.254 74.167  1.215 1.00 32.18    A2
ATOM  695 C   LEU  93    36.264 76.353  4.426 1.00 36.44    A2
ATOM  696 O   LEU  93    35.473 75.917  5.256 1.00 35.17    A2
ATOM  697 N   GLU  94    37.357 77.019  4.736 1.00 38.19    A2
ATOM  698 H   GLU  94    38.022 77.167  4.035 1.00 0.00     A2
ATOM  699 CA  GLU  94    37.627 77.573  6.038 1.00 42.71    A2
ATOM  700 CB  GLU  94    36.931 78.947  6.165 1.00 47.18    A2
ATOM  701 CG  GLU  94    37.418 80.011  5.131 1.00 56.10    A2
ATOM  702 CD  GLU  94    36.423 81.153  4.862 1.00 60.26    A2
ATOM  703 OE1 GLU  94    35.728 81.109  3.823 1.00 60.76    A2
ATOM  704 OE2 GLU  94    36.331 82.054  5.721 1.00 61.64    A2
ATOM  705 C   GLU  94    37.245 76.701  7.198 1.00 44.90    A2
ATOM  706 O   GLU  94    36.624 77.172  8.167 1.00 45.70    A2
ATOM  707 N   GLY  95    37.641 75.410  7.001 1.00 44.04    A2
ATOM  708 H   GLY  95    38.024 75.192  6.127 1.00 0.00     A2
ATOM  709 CA  GLY  95    37.519 74.310  7.981 1.00 42.49    A2
ATOM  710 C   GLY  95    36.162 73.612  8.061 1.00 42.24    A2
ATOM  711 O   GLY  95    36.028 72.596  8.739 1.00 40.02    A2
ATOM  712 N   ILE  96    35.160 74.123  7.328 1.00 42.82    A2
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FIGURE 5

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ATOM  713 H   ILE  96    35.357 74.944  6.841 1.00  0.00    A2
ATOM  714 CA  ILE  96    33.760 73.692  7.312 1.00 42.12    A2
ATOM  715 CB  ILE  96    33.665 72.233  6.800 1.00 36.33    A2
ATOM  716 CG2 ILE  96    32.248 71.768  6.789 1.00 34.79    A2
ATOM  717 CG1 ILE  96    34.091 72.157  5.374 1.00 35.35    A2
ATOM  718 CD  ILE  96    34.051 70.743  4.738 1.00 33.64    A2
ATOM  719 C   ILE  96    33.106 73.863  8.709 1.00 44.74    A2
ATOM  720 O   ILE  96    32.220 74.716  8.841 1.00 44.59    A2
ATOM  721 N   SER  97    33.467 73.154  9.780 1.00 46.84    A2
ATOM  722 H   SER  97    34.243 72.553  9.706 1.00  0.00    A2
ATOM  723 CA  SER  97    32.900 73.359 11.105 1.00 48.91    A2
ATOM  724 CB  SER  97    31.804 72.343 11.347 1.00 49.60    A2
ATOM  725 OG  SER  97    32.211 71.120 11.954 1.00 52.85    A2
ATOM  726 HG  SER  97    31.406 70.573 11.942 1.00  0.00    A2
ATOM  727 C   SER  97    34.045 73.143 12.077 1.00 50.64    A2
ATOM  728 O   SER  97    35.035 72.538 11.678 1.00 52.78    A2
ATOM  729 N   PRO  98    34.063 73.474 13.348 1.00 52.12    A2
ATOM  730 CD  PRO  98    33.002 74.170 14.016 1.00 52.90    A2
ATOM  731 CA  PRO  98    35.195 73.200 14.257 1.00 54.94    A2
ATOM  732 CB  PRO  98    34.750 73.717 15.600 1.00 54.78    A2
ATOM  733 CG  PRO  98    33.772 74.777 15.182 1.00 55.48    A2
ATOM  734 C   PRO  98    35.591 71.723 14.336 1.00 56.75    A2
ATOM  735 O   PRO  98    36.738 71.274 14.468 1.00 57.85    A2
ATOM  736 N   GLU  99    34.509 70.971 14.214 1.00 58.21    A2
ATOM  737 H   GLU  99    33.652 71.400 14.028 1.00  0.00    A2
ATOM  738 CA  GLU  99    34.543 69.537 14.281 1.00 58.48    A2
ATOM  739 CB  GLU  99    33.111 69.104 14.304 1.00 63.30    A2
ATOM  740 CG  GLU  99    32.958 67.702 14.852 1.00 71.04    A2
ATOM  741 CD  GLU  99    32.076 66.838 13.962 1.00 76.95    A2
ATOM  742 OE1 GLU  99    32.209 65.608 14.079 1.00 80.63    A2
ATOM  743 OE2 GLU  99    31.295 67.382 13.153 1.00 77.99    A2
ATOM  744 C   GLU  99    35.298 69.025 13.074 1.00 55.31    A2
ATOM  745 O   GLU  99    36.251 68.270 13.210 1.00 55.96    A2
ATOM  746 N   LEU 100    34.916 69.475 11.891 1.00 51.23    A2
ATOM  747 H   LEU 100    34.214 70.159 11.841 1.00  0.00    A2
ATOM  748 CA  LEU 100    35.577 69.052 10.678 1.00 48.08    A2
ATOM  749 CB  LEU 100    34.627 69.341  9.574 1.00 45.52    A2
ATOM  750 CG  LEU 100    33.544 68.337  9.674 1.00 45.39    A2
ATOM  751 CD1 LEU 100    32.207 68.972  9.458 1.00 46.40    A2
ATOM  752 CD2 LEU 100    33.851 67.245  8.677 1.00 47.48    A2
ATOM  753 C   LEU 100    36.956 69.629 10.368 1.00 46.77    A2
ATOM  754 O   LEU 100    37.578 69.244  9.357 1.00 46.62    A2
ATOM  755 N   GLY 101    37.441 70.505 11.272 1.00 45.40    A2
ATOM  756 H   GLY 101    36.893 70.704 12.056 1.00  0.00    A2
ATOM  757 CA  GLY 101    38.703 71.238 11.126 1.00 42.52    A2
ATOM  758 C   GLY 101    39.885 70.334 10.798 1.00 40.73    A2
ATOM  759 O   GLY 101    40.475 70.402  9.710 1.00 40.69    A2
ATOM  760 N   PRO 102    40.250 69.441 11.708 1.00 38.61    A2
ATOM  761 CD  PRO 102    39.676 69.350 13.027 1.00 39.26    A2
ATOM  762 CA  PRO 102    41.390 68.566 11.606 1.00 37.30    A2
ATOM  763 CB  PRO 102    41.294 67.690 12.775 1.00 39.36    A2
ATOM  764 CG  PRO 102    40.799 68.687 13.776 1.00 41.02    A2
ATOM  765 C   PRO 102    41.364 67.795 10.331 1.00 37.15    A2
ATOM  766 O   PRO 102    42.358 67.854  9.600 1.00 38.88    A2
ATOM  767 N   THR 103    40.223 67.167 10.045 1.00 35.46    A2
ATOM  768 H   THR 103    39.466 67.223 10.662 1.00  0.00    A2
ATOM  769 CA  THR 103    40.051 66.386  8.843 1.00 34.62    A2
ATOM  770 CB  THR 103    38.592 65.888  8.715 1.00 34.07    A2
ATOM  771 OG1 THR 103    38.356 65.240  9.936 1.00 35.43    A2
ATOM  772 HG1 THR 103    38.011 65.896 10.548 1.00  0.00    A2
ATOM  773 CG2 THR 103    38.312 64.896  7.594 1.00 31.29    A2
ATOM  774 C   THR 103    40.417 67.215  7.625 1.00 34.61    A2
ATOM  775 O   THR 103    41.091 66.665  6.738 1.00 38.16    A2
ATOM  776 N   LEU 104    40.054 68.498  7.529 1.00 32.49    A2
ATOM  777 H   LEU 104    39.504 68.923  8.229 1.00  0.00    A2
ATOM  778 CA  LEU 104    40.471 69.267  6.370 1.00 30.49    A2
ATOM  779 CB  LEU 104    39.616 70.430  6.242 1.00 33.51    A2
ATOM  780 CG  LEU 104    38.356 69.996  5.611 1.00 36.61    A2
ATOM  781 CD1 LEU 104    37.222 70.621  6.381 1.00 39.43    A2
ATOM  782 CD2 LEU 104    38.418 70.294  4.132 1.00 37.89    A2
ATOM  783 C   LEU 104    41.904 69.727  6.414 1.00 28.48    A2
ATOM  784 O   LEU 104    42.583 69.825  5.398 1.00 28.47    A2
ATOM  785 N   ASP 105    42.449 69.949  7.574 1.00 26.99    A2
ATOM  786 H   ASP 105    41.903 69.912  8.388 1.00  0.00    A2
ATOM  787 CA  ASP 105    43.822 70.307  7.613 1.00 28.67    A2
ATOM  788 CB  ASP 105    44.139 70.584  9.038 1.00 33.06    A2
ATOM  789 CG  ASP 105    43.438 71.808  9.593 1.00 35.46    A2
ATOM  790 OD1 ASP 105    43.085 72.726  8.836 1.00 38.42    A2
ATOM  791 OD2 ASP 105    43.244 71.816 10.808 1.00 39.10    A2
ATOM  792 C   ASP 105    44.701 69.206  7.032 1.00 28.90    A2
ATOM  793 O   ASP 105    45.551 69.479  6.175 1.00 29.62    A2
ATOM  794 N   THR 106    44.415 67.950  7.401 1.00 26.86    A2
ATOM  795 H   THR 106    43.674 67.826  8.029 1.00  0.00    A2
ATOM  796 CA  THR 106    45.143 66.770  6.935 1.00 24.81    A2
ATOM  797 CB  THR 106    44.558 65.456  7.477 1.00 26.03    A2
ATOM  798 OG1 THR 106    44.680 65.566  8.894 1.00 31.53    A2
ATOM  799 HG1 THR 106    44.069 66.223  9.242 1.00  0.00    A2
ATOM  800 CG2 THR 106    45.258 64.220  7.011 1.00 20.90    A2
ATOM  801 C   THR 106    45.073 66.684  5.460 1.00 23.75    A2
ATOM  802 O   THR 106    46.065 66.411  4.812 1.00 24.68    A2
ATOM  803 N   LEU 107    43.887 66.917  4.946 1.00 24.30    A2
ATOM  804 H   LEU 107    43.145 67.176  5.528 1.00  0.00    A2
ATOM  805 CA  LEU 107    43.668 66.783  3.531 1.00 27.29    A2
ATOM  806 CB  LEU 107    42.158 66.913  3.273 1.00 25.45    A2
ATOM  807 CG  LEU 107    41.642 66.888  1.863 1.00 26.24    A2
ATOM  808 CD1 LEU 107    42.095 65.649  1.158 1.00 26.41    A2
ATOM  809 CD2 LEU 107    40.140 66.925  1.914 1.00 27.62    A2
ATOM  810 C   LEU 107    44.485 67.848  2.819 1.00 28.01    A2
ATOM  811 O   LEU 107    45.154 67.555  1.823 1.00 30.72    A2
ATOM  812 N   GLN 108    44.540 69.055  3.373 1.00 28.52    A2
ATOM  813 H   GLN 108    44.030 69.221  4.194 1.00  0.00    A2
ATOM  814 CA  GLN 108    45.343 70.132  2.792 1.00 28.38    A2
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FIGURE 5

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ATOM  815 CB  GLN  108      45.138  71.363   3.630  1.00 30.15      A2
ATOM  816 CG  GLN  108      43.711  71.787   3.542  1.00 32.67      A2
ATOM  817 CD  GLN  108      43.606  73.192   4.048  1.00 35.24      A2
ATOM  818 OE1 GLN  108      43.085  73.484   5.125  1.00 36.07      A2
ATOM  819 NE2 GLN  108      44.189  74.044   3.213  1.00 33.58      A2
ATOM  820 HE21 GLN  108      44.582  73.701   2.386  1.00  0.00      A2
ATOM  821 HE22 GLN  108      44.195  74.986   3.471  1.00  0.00      A2
ATOM  822 C   GLN  108      46.840  69.842   2.675  1.00 26.40      A2
ATOM  823 O   GLN  108      47.450  69.955   1.597  1.00 27.57      A2
ATOM  824 N   LEU  109      47.388  69.473   3.833  1.00 25.81      A2
ATOM  825 H   LEU  109      46.795  69.495   4.615  1.00  0.00      A2
ATOM  826 CA  LEU  109      48.764  69.003   4.043  1.00 27.96      A2
ATOM  827 CB  LEU  109      48.951  68.637   5.513  1.00 29.41      A2
ATOM  828 CG  LEU  109      48.712  69.771   6.520  1.00 31.78      A2
ATOM  829 CD1 LEU  109      48.750  69.188   7.933  1.00 29.16      A2
ATOM  830 CD2 LEU  109      49.724  70.889   6.285  1.00 32.19      A2
ATOM  831 C   LEU  109      49.168  67.790   3.186  1.00 26.80      A2
ATOM  832 O   LEU  109      50.214  67.721   2.544  1.00 26.81      A2
ATOM  833 N   ASP  110      48.305  66.807   3.090  1.00 25.98      A2
ATOM  834 H   ASP  110      47.471  66.835   3.600  1.00  0.00      A2
ATOM  835 CA  ASP  110      48.590  65.684   2.250  1.00 23.32      A2
ATOM  836 CB  ASP  110      47.577  64.570   2.553  1.00 26.34      A2
ATOM  837 CG  ASP  110      47.905  63.878   3.894  1.00 31.10      A2
ATOM  838 OD1 ASP  110      47.070  63.093   4.323  1.00 34.98      A2
ATOM  839 OD2 ASP  110      48.958  64.107   4.535  1.00 34.06      A2
ATOM  840 C   ASP  110      48.557  66.138   0.842  1.00 21.31      A2
ATOM  841 O   ASP  110      49.493  65.711   0.165  1.00 20.63      A2
ATOM  842 N   VAL  111      47.627  66.998   0.363  1.00 20.80      A2
ATOM  843 H   VAL  111      46.900  67.310   0.944  1.00  0.00      A2
ATOM  844 CA  VAL  111      47.711  67.454  -1.019  1.00 20.44      A2
ATOM  845 CB  VAL  111      46.531  68.364  -1.376  1.00 23.60      A2
ATOM  846 CG1 VAL  111      46.615  68.946  -2.808  1.00 23.04      A2
ATOM  847 CG2 VAL  111      45.289  67.497  -1.371  1.00 24.30      A2
ATOM  848 C   VAL  111      49.006  68.224  -1.245  1.00 20.82      A2
ATOM  849 O   VAL  111      49.617  68.006  -2.303  1.00 19.22      A2
ATOM  850 N   ALA  112      49.442  69.063  -0.267  1.00 21.84      A2
ATOM  851 H   ALA  112      48.839  69.190   0.492  1.00  0.00      A2
ATOM  852 CA  ALA  112      50.708  69.805  -0.295  1.00 24.16      A2
ATOM  853 CB  ALA  112      50.861  70.561   1.011  1.00 22.69      A2
ATOM  854 C   ALA  112      51.931  68.878  -0.486  1.00 28.58      A2
ATOM  855 O   ALA  112      52.778  69.026  -1.390  1.00 32.53      A2
ATOM  856 N   ASP  113      52.086  67.852   0.343  1.00 30.21      A2
ATOM  857 H   ASP  113      51.507  67.817   1.130  1.00  0.00      A2
ATOM  858 CA  ASP  113      53.084  66.846   0.166  1.00 31.70      A2
ATOM  859 CB  ASP  113      52.706  65.659   0.953  1.00 36.31      A2
ATOM  860 CG  ASP  113      53.170  65.758   2.357  1.00 42.27      A2
ATOM  861 OD1 ASP  113      52.559  65.109   3.203  1.00 46.37      A2
ATOM  862 OD2 ASP  113      54.160  66.461   2.589  1.00 48.93      A2
ATOM  863 C   ASP  113      53.315  66.361  -1.239  1.00 32.82      A2
ATOM  864 O   ASP  113      54.433  66.308  -1.754  1.00 36.25      A2
ATOM  865 N   PHE  114      52.187  65.978  -1.830  1.00 30.94      A2
ATOM  866 H   PHE  114      51.344  66.164  -1.361  1.00  0.00      A2
ATOM  867 CA  PHE  114      52.109  65.328  -3.103  1.00 27.84      A2
ATOM  868 CB  PHE  114      50.708  64.794  -3.226  1.00 23.18      A2
ATOM  869 CG  PHE  114      50.565  63.928  -4.420  1.00 21.04      A2
ATOM  870 CD1 PHE  114      51.623  63.225  -4.938  1.00 24.05      A2
ATOM  871 CD2 PHE  114      49.369  63.914  -5.046  1.00 22.37      A2
ATOM  872 CE1 PHE  114      51.476  62.514  -6.102  1.00 24.54      A2
ATOM  873 CE2 PHE  114      49.211  63.207  -6.212  1.00 21.33      A2
ATOM  874 CZ  PHE  114      50.263  62.509  -6.741  1.00 24.71      A2
ATOM  875 C   PHE  114      52.453  66.291  -4.190  1.00 29.20      A2
ATOM  876 O   PHE  114      53.072  65.883  -5.158  1.00 30.84      A2
ATOM  877 N   ALA  115      52.057  67.554  -4.058  1.00 31.99      A2
ATOM  878 H   ALA  115      51.446  67.768  -3.317  1.00  0.00      A2
ATOM  879 CA  ALA  115      52.423  68.655  -4.952  1.00 31.29      A2
ATOM  880 CB  ALA  115      51.824  69.939  -4.420  1.00 30.65      A2
ATOM  881 C   ALA  115      53.936  68.787  -4.976  1.00 31.31      A2
ATOM  882 O   ALA  115      54.539  68.823  -6.044  1.00 30.36      A2
ATOM  883 N   THR  116      54.551  68.846  -3.813  1.00 32.20      A2
ATOM  884 H   THR  116      54.013  68.910  -2.992  1.00  0.00      A2
ATOM  885 CA  THR  116      55.998  68.897  -3.656  1.00 34.91      A2
ATOM  886 CB  THR  116      56.325  68.953  -2.150  1.00 35.78      A2
ATOM  887 OG1 THR  116      55.564  70.038  -1.576  1.00 35.58      A2
ATOM  888 HG1 THR  116      54.942  69.644  -0.939  1.00  0.00      A2
ATOM  889 CG2 THR  116      57.816  69.050  -1.921  1.00 35.48      A2
ATOM  890 C   THR  116      56.714  67.726  -4.304  1.00 37.14      A2
ATOM  891 O   THR  116      57.641  67.937  -5.066  1.00 39.27      A2
ATOM  892 N   THR  117      56.318  66.485  -4.045  1.00 39.05      A2
ATOM  893 H   THR  117      55.615  66.383  -3.369  1.00  0.00      A2
ATOM  894 CA  THR  117      56.840  65.269  -4.630  1.00 40.23      A2
ATOM  895 CB  THR  117      55.909  64.090  -4.216  1.00 39.99      A2
ATOM  896 OG1 THR  117      56.149  63.920  -2.820  1.00 41.66      A2
ATOM  897 HG1 THR  117      55.653  64.559  -2.286  1.00  0.00      A2
ATOM  898 CG2 THR  117      56.110  62.781  -4.981  1.00 38.23      A2
ATOM  899 C   THR  117      56.882  65.417  -6.134  1.00 43.42      A2
ATOM  900 O   THR  117      57.934  65.253  -6.749  1.00 46.29      A2
ATOM  901 N   ILE  118      55.763  65.777  -6.741  1.00 45.87      A2
ATOM  902 H   ILE  118      54.962  65.942  -6.200  1.00  0.00      A2
ATOM  903 CA  ILE  118      55.659  65.914  -8.182  1.00 47.97      A2
ATOM  904 CB  ILE  118      54.170  66.271  -8.452  1.00 47.69      A2
ATOM  905 CG2 ILE  118      54.041  66.930  -9.835  1.00 47.03      A2
ATOM  906 CG1 ILE  118      53.302  65.011  -8.244  1.00 44.09      A2
ATOM  907 CD  ILE  118      53.651  63.883  -9.236  1.00 43.71      A2
ATOM  908 C   ILE  118      56.647  66.932  -8.724  1.00 50.69      A2
ATOM  909 O   ILE  118      57.390  66.676  -9.681  1.00 49.98      A2
ATOM  910 N   TRP  119      56.697  68.061  -8.015  1.00 54.68      A2
ATOM  911 H   TRP  119      56.164  68.135  -7.197  1.00  0.00      A2
ATOM  912 CA  TRP  119      57.575  69.142  -8.399  1.00 58.98      A2
ATOM  913 CB  TRP  119      57.392  70.367  -7.477  1.00 59.84      A2
ATOM  914 CG  TRP  119      58.051  71.529  -8.196  1.00 62.64      A2
ATOM  915 CD2 TRP  119      57.596  72.211  -9.307  1.00 63.78      A2
ATOM  916 CE2 TRP  119      58.699  72.955  -9.643  1.00 62.55      A2
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FIGURE 5

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ATOM  917 CE3 TRP  119      56.465  72.314 -10.080  1.00 66.02      A2
ATOM  918 CD1 TRP  119      59.322  71.870  -7.863  1.00 64.12      A2
ATOM  919 NE1 TRP  119      59.680  72.727  -8.784  1.00 65.00      A2
ATOM  920 HE1 TRP  119      60.568  73.140  -8.828  1.00  0.00      A2
ATOM  921 CZ2 TRP  119      58.726  73.794 -10.714  1.00 62.90      A2
ATOM  922 CZ3 TRP  119      56.469  73.157 -11.170  1.00 65.18      A2
ATOM  923 CH2 TRP  119      57.591  73.887 -11.481  1.00 64.40      A2
ATOM  924 C   TRP  119      59.021  68.664  -8.352  1.00 61.26      A2
ATOM  925 O   TRP  119      59.748  68.788  -9.343  1.00 62.12      A2
ATOM  926 N   GLN  120      59.447  68.065  -7.249  1.00 62.91      A2
ATOM  927 H   GLN  120      58.811  67.961  -6.519  1.00  0.00      A2
ATOM  928 CA  GLN  120      60.786  67.504  -7.113  1.00 65.16      A2
ATOM  929 CB  GLN  120      60.900  66.800  -5.780  1.00 66.56      A2
ATOM  930 CG  GLN  120      60.627  67.678  -4.582  1.00 67.18      A2
ATOM  931 CD  GLN  120      60.725  66.907  -3.284  1.00 67.77      A2
ATOM  932 OE1 GLN  120      61.221  67.465  -2.319  1.00 69.31      A2
ATOM  933 NE2 GLN  120      60.305  65.654  -3.129  1.00 67.39      A2
ATOM  934 HE21 GLN  120      59.903  65.174  -3.877  1.00  0.00      A2
ATOM  935 HE22 GLN  120      60.441  65.282  -2.234  1.00  0.00      A2
ATOM  936 C   GLN  120      61.169  66.509  -8.222  1.00 66.22      A2
ATOM  937 O   GLN  120      62.326  66.421  -8.662  1.00 66.50      A2
ATOM  938 N   GLN  121      60.202  65.745  -8.706  1.00 67.10      A2
ATOM  939 H   GLN  121      59.307  65.754  -8.303  1.00  0.00      A2
ATOM  940 CA  GLN  121      60.480  64.878  -9.812  1.00 68.66      A2
ATOM  941 CB  GLN  121      59.292  63.971 -10.070  1.00 67.96      A2
ATOM  942 CG  GLN  121      59.614  62.937 -11.128  1.00 68.89      A2
ATOM  943 CD  GLN  121      60.940  62.236 -10.852  1.00 71.37      A2
ATOM  944 OE1 GLN  121      61.212  61.706  -9.777  1.00 71.70      A2
ATOM  945 NE2 GLN  121      61.879  62.262 -11.786  1.00 74.41      A2
ATOM  946 HE21 GLN  121      61.707  62.729 -12.627  1.00  0.00      A2
ATOM  947 HE22 GLN  121      62.736  61.859 -11.541  1.00  0.00      A2
ATOM  948 C   GLN  121      60.760  65.743 -11.045  1.00 70.48      A2
ATOM  949 O   GLN  121      61.671  65.436 -11.827  1.00 70.94      A2
ATOM  950 N   MET  122      60.019  66.846 -11.236  1.00 71.67      A2
ATOM  951 H   MET  122      59.351  67.087 -10.555  1.00  0.00      A2
ATOM  952 CA  MET  122      60.190  67.688 -12.412  1.00 72.62      A2
ATOM  953 CB  MET  122      59.173  68.810 -12.448  1.00 73.12      A2
ATOM  954 CG  MET  122      57.880  68.343 -13.083  1.00 73.64      A2
ATOM  955 SD  MET  122      56.669  69.662 -13.295  1.00 75.44      A2
ATOM  956 CE  MET  122      55.695  69.349 -11.861  1.00 76.43      A2
ATOM  957 C   MET  122      61.566  68.281 -12.411  1.00 73.22      A2
ATOM  958 O   MET  122      62.240  68.287 -13.441  1.00 73.03      A2
ATOM  959 N   GLU  123      61.991  68.697 -11.223  1.00 74.74      A2
ATOM  960 H   GLU  123      61.372  68.617 -10.466  1.00  0.00      A2
ATOM  961 CA  GLU  123      63.305  69.262 -11.018  1.00 75.95      A2
ATOM  962 CB  GLU  123      63.484  69.665  -9.597  1.00 75.72      A2
ATOM  963 CG  GLU  123      62.644  70.906  -9.500  1.00 79.11      A2
ATOM  964 CD  GLU  123      62.651  71.529  -8.122  1.00 83.02      A2
ATOM  965 OE1 GLU  123      62.741  72.763  -8.057  1.00 84.15      A2
ATOM  966 OE2 GLU  123      62.543  70.789  -7.133  1.00 84.45      A2
ATOM  967 C   GLU  123      64.381  68.280 -11.386  1.00 77.17      A2
ATOM  968 O   GLU  123      65.092  68.558 -12.356  1.00 78.22      A2
ATOM  969 N   GLU  124      64.504  67.110 -10.765  1.00 77.66      A2
ATOM  970 H   GLU  124      63.867  66.852 -10.060  1.00  0.00      A2
ATOM  971 CA  GLU  124      65.574  66.215 -11.167  1.00 78.47      A2
ATOM  972 CB  GLU  124      65.600  65.051 -10.195  1.00 80.79      A2
ATOM  973 CG  GLU  124      64.387  64.132 -10.150  1.00 84.29      A2
ATOM  974 CD  GLU  124      64.375  63.248  -8.908  1.00 85.51      A2
ATOM  975 OE1 GLU  124      64.733  63.729  -7.824  1.00 86.84      A2
ATOM  976 OE2 GLU  124      64.006  62.075  -9.024  1.00 86.39      A2
ATOM  977 C   GLU  124      65.534  65.705 -12.612  1.00 78.01      A2
ATOM  978 O   GLU  124      66.480  65.057 -13.060  1.00 78.91      A2
ATOM  979 N   LEU  125      64.460  65.943 -13.363  1.00 77.11      A2
ATOM  980 H   LEU  125      63.666  66.340 -12.945  1.00  0.00      A2
ATOM  981 CA  LEU  125      64.387  65.583 -14.771  1.00 76.23      A2
ATOM  982 CB  LEU  125      63.061  64.832 -14.952  1.00 76.88      A2
ATOM  983 CG  LEU  125      62.392  64.382 -16.263  1.00 76.64      A2
ATOM  984 CD1 LEU  125      63.350  63.754 -17.276  1.00 76.67      A2
ATOM  985 CD2 LEU  125      61.309  63.402 -15.839  1.00 75.89      A2
ATOM  986 C   LEU  125      64.506  66.827 -15.648  1.00 75.84      A2
ATOM  987 O   LEU  125      64.360  66.788 -16.871  1.00 75.36      A2
ATOM  988 N   GLY  126      64.759  67.968 -15.027  1.00 75.90      A2
ATOM  989 H   GLY  126      64.741  67.976 -14.056  1.00  0.00      A2
ATOM  990 CA  GLY  126      64.968  69.213 -15.736  1.00 77.58      A2
ATOM  991 C   GLY  126      63.697  69.814 -16.330  1.00 78.63      A2
ATOM  992 O   GLY  126      63.735  70.736 -17.146  1.00 78.55      A2
ATOM  993 N   MET  127      62.524  69.343 -15.933  1.00 80.08      A2
ATOM  994 H   MET  127      62.522  68.603 -15.293  1.00  0.00      A2
ATOM  995 CA  MET  127      61.266  69.902 -16.415  1.00 81.46      A2
ATOM  996 CB  MET  127      60.191  68.802 -16.361  1.00 81.86      A2
ATOM  997 CG  MET  127      60.708  67.599 -17.147  1.00 82.66      A2
ATOM  998 SD  MET  127      59.682  66.115 -17.282  1.00 84.70      A2
ATOM  999 CE  MET  127      60.236  65.620 -18.900  1.00 83.23      A2
ATOM 1000 C   MET  127      60.847  71.131 -15.599  1.00 82.18      A2
ATOM 1001 OT1 MET  127      60.116  71.958 -16.142  1.00 83.86      A2
ATOM 1002 OT2 MET  127      61.267  71.285 -14.446  1.00 82.04      A2
ATOM 1003 CB  MET  138      39.323  80.595  -4.492  1.00 59.39      A3
ATOM 1004 CG  MET  138      40.123  79.298  -4.421  1.00 57.97      A3
ATOM 1005 SD  MET  138      40.561  78.973  -6.145  1.00 60.85      A3
ATOM 1006 CE  MET  138      41.129  77.310  -6.351  1.00 61.48      A3
ATOM 1007 C   MET  138      37.021  81.072  -5.454  1.00 60.26      A3
ATOM 1008 O   MET  138      36.832  82.262  -5.181  1.00 62.98      A3
ATOM 1009 HT1 MET  138      38.497  82.600  -6.075  1.00  0.00      A3
ATOM 1010 HT2 MET  138      38.313  81.757  -7.529  1.00  0.00      A3
ATOM 1011 N   MET  138      38.839  81.784  -6.639  1.00 60.49      A3
ATOM 1012 HT3 MET  138      39.865  81.816  -6.768  1.00  0.00      A3
ATOM 1013 CA  MET  138      38.445  80.672  -5.787  1.00 60.51      A3
ATOM 1014 N   PRO  139      35.995  80.242  -5.612  1.00 57.82      A3
ATOM 1015 CD  PRO  139      36.028  79.060  -6.448  1.00 58.10      A3
ATOM 1016 CA  PRO  139      34.654  80.538  -5.142  1.00 54.67      A3
ATOM 1017 CB  PRO  139      33.870  79.323  -5.525  1.00 54.54      A3
ATOM 1018 CG  PRO  139      34.945  78.290  -5.755  1.00 58.26      A3
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FIGURE 5

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ATOM 1019 C  PRO 139   34.588 80.875 -3.664 1.00 52.24  A3
ATOM 1020 O  PRO 139   35.507 80.623 -2.882 1.00 51.89  A3
ATOM 1021 N  ALA 140   33.499 81.547 -3.342 1.00 49.86  A3
ATOM 1022 H  ALA 140   32.789 81.676 -4.005 1.00 0.00   A3
ATOM 1023 CA ALA 140   33.234 81.926 -1.994 1.00 49.39  A3
ATOM 1024 CB ALA 140   32.966 83.413 -1.895 1.00 49.94  A3
ATOM 1025 C  ALA 140   31.978 81.153 -1.590 1.00 49.25  A3
ATOM 1026 O  ALA 140   30.889 81.162 -2.205 1.00 49.06  A3
ATOM 1027 N  PHE 141   32.293 80.442 -0.506 1.00 47.48  A3
ATOM 1028 H  PHE 141   33.190 80.550 -0.122 1.00 0.00   A3
ATOM 1029 CA PHE 141   31.401 79.552 0.208 1.00 45.66  A3
ATOM 1030 CB PHE 141   32.215 78.305 0.792 1.00 40.28  A3
ATOM 1031 CG PHE 141   32.684 77.404 -0.349 1.00 35.35  A3
ATOM 1032 CD1 PHE 141  31.800 76.591 -1.006 1.00 34.39  A3
ATOM 1033 CD2 PHE 141  33.966 77.497 -0.830 1.00 37.69  A3
ATOM 1034 CE1 PHE 141  32.174 75.895 -2.133 1.00 34.00  A3
ATOM 1035 CE2 PHE 141  34.358 76.807 -1.956 1.00 36.69  A3
ATOM 1036 CZ PHE 141   33.449 76.001 -2.614 1.00 37.29  A3
ATOM 1037 C  PHE 141   31.003 80.580 1.242 1.00 46.54  A3
ATOM 1038 O  PHE 141   31.584 80.664 2.317 1.00 48.26  A3
ATOM 1039 N  ALA 142   30.067 81.452 0.843 1.00 47.38  A3
ATOM 1040 H  ALA 142   29.624 81.295 -0.020 1.00 0.00   A3
ATOM 1041 CA ALA 142   29.581 82.564 1.668 1.00 46.06  A3
ATOM 1042 CB ALA 142   28.731 83.546 0.879 1.00 45.04  A3
ATOM 1043 C  ALA 142   28.703 82.132 2.802 1.00 45.27  A3
ATOM 1044 O  ALA 142   28.343 83.002 3.584 1.00 47.38  A3
ATOM 1045 N  SER 143   28.318 80.860 2.899 1.00 43.36  A3
ATOM 1046 H  SER 143   28.724 80.201 2.303 1.00 0.00   A3
ATOM 1047 CA SER 143   27.377 80.392 3.897 1.00 41.94  A3
ATOM 1048 CB SER 143   26.036 80.129 3.181 1.00 44.17  A3
ATOM 1049 OG SER 143   25.323 78.918 3.536 1.00 48.18  A3
ATOM 1050 HG SER 143   24.455 78.974 3.098 1.00 0.00   A3
ATOM 1051 C  SER 143   27.877 79.145 4.602 1.00 39.79  A3
ATOM 1052 O  SER 143   28.763 78.452 4.132 1.00 38.50  A3
ATOM 1053 N  ALA 144   27.218 78.775 5.683 1.00 39.10  A3
ATOM 1054 H  ALA 144   26.449 79.312 5.960 1.00 0.00   A3
ATOM 1055 CA ALA 144   27.566 77.586 6.411 1.00 39.22  A3
ATOM 1056 CB ALA 144   26.982 77.598 7.802 1.00 36.97  A3
ATOM 1057 C  ALA 144   26.964 76.420 5.627 1.00 41.58  A3
ATOM 1058 O  ALA 144   27.706 75.448 5.444 1.00 42.07  A3
ATOM 1059 N  PHE 145   25.719 76.407 5.076 1.00 40.77  A3
ATOM 1060 H  PHE 145   25.149 77.203 5.110 1.00 0.00   A3
ATOM 1061 CA PHE 145   25.307 75.234 4.312 1.00 39.31  A3
ATOM 1062 CB PHE 145   23.877 75.396 3.798 1.00 36.46  A3
ATOM 1063 CG PHE 145   23.477 74.452 2.641 1.00 31.91  A3
ATOM 1064 CD1 PHE 145  23.579 74.900 1.323 1.00 29.02  A3
ATOM 1065 CD2 PHE 145  23.013 73.185 2.916 1.00 29.40  A3
ATOM 1066 CE1 PHE 145  23.225 74.100 0.277 1.00 28.34  A3
ATOM 1067 CE2 PHE 145  22.661 72.389 1.858 1.00 28.80  A3
ATOM 1068 CZ PHE 145   22.764 72.831 0.549 1.00 30.58  A3
ATOM 1069 C  PHE 145   26.266 75.071 3.120 1.00 40.44  A3
ATOM 1070 O  PHE 145   26.556 73.938 2.697 1.00 40.55  A3
ATOM 1071 N  GLN 146   26.745 76.232 2.619 1.00 39.11  A3
ATOM 1072 H  GLN 146   26.437 77.073 3.015 1.00 0.00   A3
ATOM 1073 CA GLN 146   27.660 76.263 1.511 1.00 38.01  A3
ATOM 1074 CB GLN 146   27.907 77.644 1.054 1.00 38.92  A3
ATOM 1075 CG GLN 146   26.884 78.066 0.049 1.00 44.26  A3
ATOM 1076 CD GLN 146   27.171 79.440 -0.522 1.00 45.47  A3
ATOM 1077 OE1 GLN 146  27.851 80.253 0.083 1.00 47.57  A3
ATOM 1078 NE2 GLN 146  26.689 79.793 -1.692 1.00 47.50  A3
ATOM 1079 HE21 GLN 146 26.149 79.149 -2.190 1.00 0.00   A3
ATOM 1080 HE22 GLN 146 26.913 80.690 -2.021 1.00 0.00   A3
ATOM 1081 C  GLN 146   29.005 75.670 1.836 1.00 47.25  A3
ATOM 1082 O  GLN 146   29.634 75.093 0.950 1.00 48.28  A3
ATOM 1083 N  ARG 147   29.511 75.775 3.054 1.00 46.57  A3
ATOM 1084 H  ARG 147   29.044 76.300 3.738 1.00 0.00   A3
ATOM 1085 CA ARG 147   30.798 75.180 3.357 1.00 35.68  A3
ATOM 1086 CB ARG 147   31.299 75.574 4.713 1.00 37.12  A3
ATOM 1087 CG ARG 147   31.730 77.016 4.697 1.00 42.68  A3
ATOM 1088 CD ARG 147   32.034 77.494 6.093 1.00 49.54  A3
ATOM 1089 NE ARG 147   32.674 78.774 5.877 1.00 58.21  A3
ATOM 1090 HE ARG 147   32.475 79.252 5.045 1.00 0.00   A3
ATOM 1091 CZ ARG 147   33.519 79.373 6.742 1.00 62.77  A3
ATOM 1092 NH1 ARG 147  33.905 78.868 7.936 1.00 63.96  A3
ATOM 1093 HH11 ARG 147 34.545 79.379 8.510 1.00 0.00   A3
ATOM 1094 HH12 ARG 147 33.561 77.980 8.239 1.00 0.00   A3
ATOM 1095 NH2 ARG 147  33.960 80.584 6.403 1.00 64.80  A3
ATOM 1096 HH21 ARG 147 34.599 81.069 6.999 1.00 0.00   A3
ATOM 1097 HH22 ARG 147 33.665 80.996 5.541 1.00 0.00   A3
ATOM 1098 C  ARG 147   30.570 73.702 3.337 1.00 34.91  A3
ATOM 1099 O  ARG 147   31.233 73.050 2.539 1.00 34.56  A3
ATOM 1100 N  ALA 148   29.544 73.194 4.040 1.00 33.44  A3
ATOM 1101 H  ALA 148   28.926 73.818 4.482 1.00 0.00   A3
ATOM 1102 CA ALA 148   29.358 71.754 4.172 1.00 33.92  A3
ATOM 1103 CB ALA 148   28.217 71.426 5.163 1.00 32.85  A3
ATOM 1104 C  ALA 148   29.077 71.095 2.845 1.00 33.40  A3
ATOM 1105 O  ALA 148   29.765 70.141 2.457 1.00 34.31  A3
ATOM 1106 N  ALA 149   28.169 71.657 2.077 1.00 32.60  A3
ATOM 1107 H  ALA 149   27.662 72.424 2.411 1.00 0.00   A3
ATOM 1108 CA ALA 149   27.890 71.134 0.757 1.00 32.76  A3
ATOM 1109 CB ALA 149   26.595 71.774 0.299 1.00 31.91  A3
ATOM 1110 C  ALA 149   29.032 71.381 -0.258 1.00 33.75  A3
ATOM 1111 O  ALA 149   29.208 70.661 -1.264 1.00 34.49  A3
ATOM 1112 N  GLY 150   29.867 72.401 -0.052 1.00 34.58  A3
ATOM 1113 H  GLY 150   29.724 73.035 0.682 1.00 0.00   A3
ATOM 1114 CA GLY 150   31.017 72.608 -0.913 1.00 41.79  A3
ATOM 1115 C  GLY 150   32.113 71.629 -0.478 1.00 41.39  A3
ATOM 1116 O  GLY 150   32.997 71.261 -1.265 1.00 41.77  A3
ATOM 1117 N  GLY 151   32.075 71.161 0.773 1.00 29.84  A3
ATOM 1118 H  GLY 151   31.412 71.524 1.394 1.00 0.00   A3
ATOM 1119 CA GLY 151   33.018 70.166 1.243 1.00 42.16  A3
ATOM 1120 C  GLY 151   32.764 68.909 0.409 1.00 44.98  A3
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EP 0 612 846 A1

FIGURE 5

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ATOM  1121  O   GLY  151      33.664  68.501  -0.349  1.00 35.66      A3
ATOM  1122  N   VAL  152      31.486  68.418   0.451  1.00 31.87      A3
ATOM  1123  H   VAL  152      30.867  68.906   1.040  1.00  0.00      A3
ATOM  1124  CA  VAL  152      30.978  67.240  -0.275  1.00 29.61      A3
ATOM  1125  CB  VAL  152      29.419  67.145  -0.125  1.00 27.63      A3
ATOM  1126  CG1 VAL  152      28.883  66.035  -0.976  1.00 27.37      A3
ATOM  1127  CG2 VAL  152      29.002  66.786   1.279  1.00 24.74      A3
ATOM  1128  C   VAL  152      31.351  67.294  -1.762  1.00 29.91      A3
ATOM  1129  O   VAL  152      31.805  66.329  -2.393  1.00 31.75      A3
ATOM  1130  N   LEU  153      31.236  68.452  -2.361  1.00 29.26      A3
ATOM  1131  H   LEU  153      30.881  69.219  -1.860  1.00  0.00      A3
ATOM  1132  CA  LEU  153      31.559  68.607  -3.756  1.00 26.77      A3
ATOM  1133  CB  LEU  153      30.881  69.858  -4.160  1.00 28.22      A3
ATOM  1134  CG  LEU  153      29.943  69.894  -5.316  1.00 30.67      A3
ATOM  1135  CD1 LEU  153      28.580  69.281  -5.090  1.00 26.48      A3
ATOM  1136  CD2 LEU  153      29.741  71.365  -5.496  1.00 34.46      A3
ATOM  1137  C   LEU  153.     33.032  68.628  -4.111  1.00 26.08      A3
ATOM  1138  O   LEU  153      33.419  68.187  -5.212  1.00 26.78      A3
ATOM  1139  N   VAL  154      33.902  69.180  -3.269  1.00 26.12      A3
ATOM  1140  H   VAL  154      33.589  69.557  -2.416  1.00  0.00      A3
ATOM  1141  CA  VAL  154      35.330  69.259  -3.611  1.00 26.23      A3
ATOM  1142  CB  VAL  154      36.057  70.299  -2.692  1.00 26.51      A3
ATOM  1143  CG1 VAL  154      37.578  70.188  -2.942  1.00 25.01      A3
ATOM  1144  CG2 VAL  154      35.528  71.728  -2.945  1.00 27.82      A3
ATOM  1145  C   VAL  154      35.933  67.850  -3.375  1.00 26.80      A3
ATOM  1146  O   VAL  154      36.678  67.363  -4.229  1.00 26.27      A3
ATOM  1147  N   ALA  155      35.635  67.241  -2.199  1.00 24.76      A3
ATOM  1148  H   ALA  155      35.084  67.758  -1.570  1.00  0.00      A3
ATOM  1149  CA  ALA  155      36.095  65.940  -1.782  1.00 25.21      A3
ATOM  1150  CB  ALA  155      35.463  65.572  -0.457  1.00 25.25      A3
ATOM  1151  C   ALA  155      35.708  64.946  -2.841  1.00 26.94      A3
ATOM  1152  O   ALA  155      36.594  64.288  -3.398  1.00 26.76      A3
ATOM  1153  N   SER  156      34.450  64.982  -3.282  1.00 29.96      A3
ATOM  1154  H   SER  156      33.790  65.577  -2.868  1.00  0.00      A3
ATOM  1155  CA  SER  156      34.034  64.105  -4.354  1.00 32.17      A3
ATOM  1156  CB  SER  156      32.531  64.319  -4.544  1.00 34.23      A3
ATOM  1157  OG  SER  156      32.000  64.195  -5.879  1.00 39.35      A3
ATOM  1158  HG  SER  156      31.120  63.815  -5.851  1.00  0.00      A3
ATOM  1159  C   SER  156      34.845  64.338  -5.632  1.00 33.46      A3
ATOM  1160  O   SER  156      35.411  63.380  -6.174  1.00 34.62      A3
ATOM  1161  N   HIS  157      35.054  65.576  -6.133  1.00 33.90      A3
ATOM  1162  H   HIS  157      34.771  66.349  -5.605  1.00  0.00      A3
ATOM  1163  CA  HIS  157      35.821  65.773  -7.383  1.00 31.19      A3
ATOM  1164  CB  HIS  157      35.707  67.209  -7.900  1.00 32.59      A3
ATOM  1165  CG  HIS  157      34.369  67.449  -8.566  1.00 31.11      A3
ATOM  1166  CD2 HIS  157      34.127  67.394  -9.928  1.00 30.78      A3
ATOM  1167  ND1 HIS  157      33.223  67.666  -7.942  1.00 32.36      A3
ATOM  1168  HD1 HIS  157      33.080  67.773  -6.979  1.00  0.00      A3
ATOM  1169  CE1 HIS  157      32.293  67.732  -8.875  1.00 32.01      A3
ATOM  1170  NE2 HIS  157      32.838  67.571 -10.060  1.00 29.18      A3
ATOM  1171  HE2 HIS  157      32.327  67.621 -10.895  1.00  0.00      A3
ATOM  1172  C   HIS  157      37.291  65.476  -7.269  1.00 29.68      A3
ATOM  1173  O   HIS  157      37.950  65.059  -8.219  1.00 29.65      A3
ATOM  1174  N   LEU  158      37.801  65.669  -6.071  1.00 29.24      A3
ATOM  1175  H   LEU  158      37.213  65.901  -5.326  1.00  0.00      A3
ATOM  1176  CA  LEU  158      39.216  65.479  -5.826  1.00 31.94      A3
ATOM  1177  CB  LEU  158      39.609  65.949  -4.373  1.00 28.65      A3
ATOM  1178  CG  LEU  158      41.008  65.751  -3.859  1.00 24.32      A3
ATOM  1179  CD1 LEU  158      41.990  66.378  -4.776  1.00 20.87      A3
ATOM  1180  CD2 LEU  158      41.099  66.330  -2.477  1.00 24.86      A3
ATOM  1181  C   LEU  158      39.468  63.994  -6.027  1.00 31.46      A3
ATOM  1182  O   LEU  158      40.298  63.609  -6.844  1.00 30.58      A3
ATOM  1183  N   GLN  159      38.652  63.225  -5.340  1.00 33.54      A3
ATOM  1184  H   GLN  159      38.011  63.676  -4.748  1.00  0.00      A3
ATOM  1185  CA  GLN  159      38.594  61.792  -5.447  1.00 35.73      A3
ATOM  1186  CB  GLN  159      37.308  61.492  -4.813  1.00 37.26      A3
ATOM  1187  CG  GLN  159      37.064  60.063  -4.520  1.00 45.01      A3
ATOM  1188  CD  GLN  159      37.755  59.611  -3.256  1.00 46.24      A3
ATOM  1189  OE1 GLN  159      38.142  58.443  -3.232  1.00 48.29      A3
ATOM  1190  NE2 GLN  159      37.936  60.456  -2.224  1.00 47.82      A3
ATOM  1191 HE21 GLN  159      37.575  61.364  -2.289  1.00  0.00      A3
ATOM  1192 HE22 GLN  159      38.412  60.101  -1.447  1.00  0.00      A3
ATOM  1193  C   GLN  159      38.686  61.381  -6.921  1.00 36.24      A3
ATOM  1194  O   GLN  159      39.632  60.690  -7.326  1.00 38.97      A3
ATOM  1195  N   SER  160      37.824  61.896  -7.796  1.00 35.48      A3
ATOM  1196  H   SER  160      37.142  62.540  -7.498  1.00  0.00      A3
ATOM  1197  CA  SER  160      37.869  61.564  -9.203  1.00 34.96      A3
ATOM  1198  CB  SER  160      36.645  62.100  -9.863  1.00 37.54      A3
ATOM  1199  OG  SER  160      35.587  62.434  -8.942  1.00 44.83      A3
ATOM  1200  HG  SER  160      35.340  61.689  -8.387  1.00  0.00      A3
ATOM  1201  C   SER  160      39.090  62.095  -9.922  1.00 31.65      A3
ATOM  1202  O   SER  160      39.605  61.382 -10.785  1.00 35.42      A3
ATOM  1203  N   PHE  161      39.615  63.293  -9.595  1.00 33.82      A3
ATOM  1204  H   PHE  161      39.203  63.796  -8.864  1.00  0.00      A3
ATOM  1205  CA  PHE  161      40.820  63.850 -10.218  1.00 31.24      A3
ATOM  1206  CB  PHE  161      41.110  65.254  -9.629  1.00 28.28      A3
ATOM  1207  CG  PHE  161      42.455  65.881 -10.062  1.00 24.92      A3
ATOM  1208  CD1 PHE  161      42.696  66.228 -11.389  1.00 22.98      A3
ATOM  1209  CD2 PHE  161      43.464  66.021  -9.135  1.00 23.63      A3
ATOM  1210  CE1 PHE  161      43.941  66.695 -11.767  1.00 21.06      A3
ATOM  1211  CE2 PHE  161      44.701  66.495  -9.528  1.00 20.28      A3
ATOM  1212  CZ  PHE  161      44.939  66.826 -10.832  1.00 17.04      A3
ATOM  1213  C   PHE  161      42.008  62.907  -9.943  1.00 31.77      A3
ATOM  1214  O   PHE  161      42.786  62.579 -10.845  1.00 32.63      A3
ATOM  1215  N   LEU  162      42.117  62.434  -8.690  1.00 31.67      A3
ATOM  1216  H   LEU  162      41.420  62.691  -8.054  1.00  0.00      A3
ATOM  1217  CA  LEU  162      43.186  61.574  -8.232  1.00 31.29      A3
ATOM  1218  CB  LEU  162      43.204  61.433  -6.743  1.00 25.84      A3
ATOM  1219  CG  LEU  162      43.693  62.674  -6.003  1.00 26.02      A3
ATOM  1220  CD1 LEU  162      43.594  62.455  -4.516  1.00 25.74      A3
ATOM  1221  CD2 LEU  162      45.107  62.994  -6.415  1.00 27.04      A3
ATOM  1222  C   LEU  162      44.061  60.212  -8.813  1.00 34.24      A3
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FIGURE 5

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ATOM  1223  O   LEU   162      44.107  59.654  -9.070  1.00 36.51      A3
ATOM  1224  N   GLU   163      41.926  59.589  -9.082  1.00 37.24      A3
ATOM  1225  H   GLU   163      41.072  60.002  -8.826  1.00  0.00      A3
ATOM  1226  CA  GLU   163      41.975  58.327  -9.771  1.00 40.47      A3
ATOM  1227  CB  GLU   163      40.566  57.716  -9.835  1.00 45.38      A3
ATOM  1228  CG  GLU   163      40.264  56.975  -8.526  1.00 51.84      A3
ATOM  1229  CD  GLU   163      41.291  55.889  -8.126  1.00 57.97      A3
ATOM  1230  OE1 GLU   163      40.897  54.722  -8.092  1.00 62.01      A3
ATOM  1231  OE2 GLU   163      42.466  56.180  -7.832  1.00 59.17      A3
ATOM  1232  C   GLU   163      42.586  58.430 -11.142  1.00 41.34      A3
ATOM  1233  O   GLU   163      43.456  57.633 -11.486  1.00 42.17      A3
ATOM  1234  N   VAL   164      42.257  59.436 -11.920  1.00 42.28      A3
ATOM  1235  H   VAL   164      41.589  60.091 -11.615  1.00  0.00      A3
ATOM  1236  CA  VAL   164      42.911  59.609 -13.187  1.00 44.13      A3
ATOM  1237  CB  VAL   164      42.207  60.711 -13.940  1.00 45.52      A3
ATOM  1238  CG1 VAL   164      42.892  60.975 -15.278  1.00 48.79      A3
ATOM  1239  CG2 VAL   164      40.786  60.269 -14.226  1.00 46.09      A3
ATOM  1240  C   VAL   164      44.386  59.933 -12.991  1.00 46.13      A3
ATOM  1241  O   VAL   164      45.192  59.473 -13.794  1.00 45.99      A3
ATOM  1242  N   SER   165      44.879  60.677 -12.006  1.00 49.51      A3
ATOM  1243  H   SER   165      44.287  61.173 -11.396  1.00  0.00      A3
ATOM  1244  CA  SER   165      46.325  60.845 -11.895  1.00 53.44      A3
ATOM  1245  CB  SER   165      46.715  61.796 -10.775  1.00 54.77      A3
ATOM  1246  OG  SER   165      46.049  61.618  -9.530  1.00 59.99      A3
ATOM  1247  HG  SER   165      45.997  60.694  -9.261  1.00  0.00      A3
ATOM  1248  C   SER   165      46.958  59.502 -11.630  1.00 55.15      A3
ATOM  1249  O   SER   165      48.028  59.227 -12.148  1.00 55.02      A3
ATOM  1250  N   TYR   166      46.239  58.645 -10.900  1.00 58.57      A3
ATOM  1251  H   TYR   166      45.374  58.948 -10.549  1.00  0.00      A3
ATOM  1252  CA  TYR   166      46.617  57.273 -10.625  1.00 61.42      A3
ATOM  1253  CB  TYR   166      45.543  56.653  -9.680  1.00 64.05      A3
ATOM  1254  CG  TYR   166      45.502  55.138  -9.682  1.00 69.00      A3
ATOM  1255  CD1 TYR   166      44.389  54.501 -10.185  1.00 71.64      A3
ATOM  1256  CE1 TYR   166      44.367  53.130 -10.283  1.00 73.15      A3
ATOM  1257  CD2 TYR   166      46.594  54.409  -9.257  1.00 71.27      A3
ATOM  1258  CE2 TYR   166      46.584  53.040  -9.346  1.00 72.92      A3
ATOM  1259  CZ  TYR   166      45.468  52.417  -9.862  1.00 75.71      A3
ATOM  1260  OH  TYR   166      45.474  51.038 -10.016  1.00 80.61      A3
ATOM  1261  HH  TYR   166      44.571  50.736 -10.134  1.00  0.00      A3
ATOM  1262  C   TYR   166      46.712  56.567 -11.987  1.00 62.34      A3
ATOM  1263  O   TYR   166      47.766  55.981 -12.282  1.00 63.25      A3
ATOM  1264  N   ALA   167      45.727  56.622 -12.884  1.00 61.27      A3
ATOM  1265  H   ALA   167      44.893  57.089 -12.678  1.00  0.00      A3
ATOM  1266  CA  ALA   167      45.933  55.982 -14.159  1.00 61.47      A3
ATOM  1267  CB  ALA   167      44.608  55.904 -14.904  1.00 60.98      A3
ATOM  1268  C   ALA   167      46.982  56.694 -15.020  1.00 62.19      A3
ATOM  1269  O   ALA   167      47.719  56.000 -15.734  1.00 62.63      A3
ATOM  1270  N   VAL   168      47.210  58.011 -14.991  1.00 63.37      A3
ATOM  1271  H   VAL   168      46.756  58.570 -14.330  1.00  0.00      A3
ATOM  1272  CA  VAL   168      48.174  58.593 -15.923  1.00 65.62      A3
ATOM  1273  CB  VAL   168      48.061  60.121 -16.131  1.00 66.30      A3
ATOM  1274  CG1 VAL   168      46.687  60.431 -16.706  1.00 66.78      A3
ATOM  1275  CG2 VAL   168      48.278  60.879 -14.840  1.00 68.47      A3
ATOM  1276  C   VAL   168      49.579  58.339 -15.469  1.00 66.45      A3
ATOM  1277  O   VAL   168      50.458  58.183 -16.302  1.00 66.22      A3
ATOM  1278  N   LEU   169      49.823  58.241 -14.177  1.00 68.83      A3
ATOM  1279  H   LEU   169      49.102  58.404 -13.536  1.00  0.00      A3
ATOM  1280  CA  LEU   169      51.141  57.899 -13.695  1.00 71.81      A3
ATOM  1281  CB  LEU   169      51.249  58.228 -12.188  1.00 71.54      A3
ATOM  1282  CG  LEU   169      51.137  59.732 -11.813  1.00 70.68      A3
ATOM  1283  CD1 LEU   169      51.187  59.826 -10.298  1.00 69.39      A3
ATOM  1284  CD2 LEU   169      52.223  60.580 -12.491  1.00 68.49      A3
ATOM  1285  C   LEU   169      51.333  56.414 -13.979  1.00 73.61      A3
ATOM  1286  O   LEU   169      52.408  56.013 -14.429  1.00 74.75      A3
ATOM  1287  N   ARG   170      50.309  55.583 -13.819  1.00 75.45      A3
ATOM  1288  H   ARG   170      49.488  55.923 -13.399  1.00  0.00      A3
ATOM  1289  CA  ARG   170      50.364  54.179 -14.199  1.00 78.17      A3
ATOM  1290  CB  ARG   170      48.944  53.642 -14.004  1.00 78.45      A3
ATOM  1291  CG  ARG   170      48.394  52.506 -14.871  1.00 78.17      A3
ATOM  1292  CD  ARG   170      48.744  51.181 -14.271  1.00 77.25      A3
ATOM  1293  NE  ARG   170      48.123  51.120 -12.970  1.00 76.15      A3
ATOM  1294  HE  ARG   170      47.245  51.528 -12.824  1.00  0.00      A3
ATOM  1295  CZ  ARG   170      48.758  50.547 -11.970  1.00 76.14      A3
ATOM  1296  NH1 ARG   170      49.973  50.017 -12.112  1.00 76.84      A3
ATOM  1297 HH11 ARG   170      50.441  50.030 -12.994  1.00  0.00      A3
ATOM  1298 HH12 ARG   170      50.406  49.570 -11.329  1.00  0.00      A3
ATOM  1299  NH2 ARG   170      48.147  50.492 -10.806  1.00 77.02      A3
ATOM  1300 HH21 ARG   170      47.237  50.890 -10.714  1.00  0.00      A3
ATOM  1301 HH22 ARG   170      48.586  50.052 -10.023  1.00  0.00      A3
ATOM  1302  C   ARG   170      50.870  54.052 -15.647  1.00 79.84      A3
ATOM  1303  O   ARG   170      51.924  53.470 -15.908  1.00 80.07      A3
ATOM  1304  N   HIS   171      50.193  54.663 -16.611  1.00 81.38      A3
ATOM  1305  H   HIS   171      49.433  55.234 -16.359  1.00  0.00      A3
ATOM  1306  CA  HIS   171      50.663  54.597 -17.970  1.00 84.03      A3
ATOM  1307  CB  HIS   171      49.590  55.054 -18.902  1.00 86.82      A3
ATOM  1308  CG  HIS   171      48.496  54.037 -19.147  1.00 90.73      A3
ATOM  1309  CD2 HIS   171      47.467  53.765 -18.272  1.00 91.35      A3
ATOM  1310  ND1 HIS   171      48.308  53.301 -20.248  1.00 92.24      A3
ATOM  1311  HD1 HIS   171      48.887  53.287 -21.044  1.00  0.00      A3
ATOM  1312  CE1 HIS   171      47.204  52.605 -20.077  1.00 92.41      A3
ATOM  1313  NE2 HIS   171      46.711  52.892 -18.891  1.00 92.59      A3
ATOM  1314  HE2 HIS   171      45.884  52.511 -18.518  1.00  0.00      A3
ATOM  1315  C   HIS   171      51.907  55.446 -18.232  1.00 85.42      A3
ATOM  1316  O   HIS   171      52.440  55.352 -19.344  1.00 85.98      A3
ATOM  1317  N   LEU   172      52.359  56.307 -17.302  1.00 86.13      A3
ATOM  1318  H   LEU   172      51.870  56.411 -16.463  1.00  0.00      A3
ATOM  1319  CA  LEU   172      53.550  57.133 -17.496  1.00 86.02      A3
ATOM  1320  CB  LEU   172      53.500  58.357 -16.607  1.00 86.31      A3
ATOM  1321  CG  LEU   172      54.022  59.658 -17.203  1.00 87.48      A3
ATOM  1322  CD1 LEU   172      53.436  59.939 -18.596  1.00 87.68      A3
ATOM  1323  CD2 LEU   172      53.645  60.778 -16.251  1.00 87.95      A3
ATOM  1324  C   LEU   172      54.813  56.357 -17.180  1.00 85.92      A3
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FIGURE 5

```
ATOM  1325 O   LEU  172    55.896 56.660 -17.692  1.00 86.23      A3
ATOM  1326 N   ALA  173    54.733 55.383 -16.282  1.00 85.49      A3
ATOM  1327 H   ALA  173    53.899 55.276 -15.769  1.00  0.00      A3
ATOM  1328 CA  ALA  173    55.856 54.497 -16.087  1.00 85.65      A3
ATOM  1329 CB  ALA  173    56.602 54.859 -14.809  1.00 85.01      A3
ATOM  1330 C   ALA  173    55.330 53.073 -16.008  1.00 86.54      A3
ATOM  1331 OT1 ALA  173    55.585 52.347 -16.971  1.00 87.21      A3
ATOM  1332 OT2 ALA  173    54.650 52.707 -15.036  1.00 87.31      A3
ATOM  1333 CB  LEU  210    45.234 42.591  25.453  1.00 52.47      B1
ATOM  1334 CG  LEU  210    43.799 42.058  25.547  1.00 51.68      B1
ATOM  1335 CD1 LEU  210    43.123 42.562  26.804  1.00 53.37      B1
ATOM  1336 CD2 LEU  210    43.050 42.453  24.303  1.00 51.37      B1
ATOM  1337 C   LEU  210    46.770 44.374  24.596  1.00 50.98      B1
ATOM  1338 O   LEU  210    46.475 45.267  23.790  1.00 51.76      B1
ATOM  1339 HT1 LEU  210    44.382 44.922  24.421  1.00  0.00      B1
ATOM  1340 HT2 LEU  210    45.157 45.974  25.414  1.00  0.00      B1
ATOM  1341 N   LEU  210    44.705 45.041  25.406  1.00 53.59      B1
ATOM  1342 HT3 LEU  210    43.855 45.012  25.997  1.00  0.00      B1
ATOM  1343 CA  LEU  210    45.730 44.038  25.676  1.00 52.35      B1
ATOM  1344 N   PRO  211    47.974 43.825  24.494  1.00 49.35      B1
ATOM  1345 CD  PRO  211    48.621 43.024  25.532  1.00 49.52      B1
ATOM  1346 CA  PRO  211    48.895 44.191  23.419  1.00 49.04      B1
ATOM  1347 CB  PRO  211    50.209 43.571  23.865  1.00 49.02      B1
ATOM  1348 CG  PRO  211    49.794 42.438  24.783  1.00 49.77      B1
ATOM  1349 C   PRO  211    48.543 43.864  21.965  1.00 48.03      B1
ATOM  1350 O   PRO  211    47.872 42.896  21.622  1.00 49.05      B1
ATOM  1351 N   GLN  212    49.032 44.675  21.051  1.00 46.52      B1
ATOM  1352 H   GLN  212    49.506 45.478  21.349  1.00  0.00      B1
ATOM  1353 CA  GLN  212    48.839 44.461  19.641  1.00 45.47      B1
ATOM  1354 CB  GLN  212    49.533 45.522  18.849  1.00 46.81      B1
ATOM  1355 CG  GLN  212    48.482 46.139  17.999  1.00 49.55      B1
ATOM  1356 CD  GLN  212    49.024 46.703  16.709  1.00 54.21      B1
ATOM  1357 OE1 GLN  212    48.429 47.672  16.232  1.00 57.72      B1
ATOM  1358 NE2 GLN  212    50.086 46.176  16.074  1.00 52.39      B1
ATOM  1359 HE21 GLN  212    50.530 45.383  16.430  1.00  0.00      B1
ATOM  1360 HE22 GLN  212    50.341 46.625  15.244  1.00  0.00      B1
ATOM  1361 C   GLN  212    49.390 43.133  19.185  1.00 44.79      B1
ATOM  1362 O   GLN  212    48.959 42.520  18.208  1.00 44.01      B1
ATOM  1363 N   SER  213    50.401 42.671  19.893  1.00 44.72      B1
ATOM  1364 H   SER  213    50.730 43.115  20.698  1.00  0.00      B1
ATOM  1365 CA  SER  213    51.025 41.424  19.521  1.00 43.76      B1
ATOM  1366 CB  SER  213    52.220 41.124  20.354  1.00 45.29      B1
ATOM  1367 OG  SER  213    51.802 41.455  21.681  1.00 52.50      B1
ATOM  1368 HG  SER  213    52.479 41.127  22.288  1.00  0.00      B1
ATOM  1369 C   SER  213    50.014 40.376  19.784  1.00 40.92      B1
ATOM  1370 O   SER  213    49.964 39.492  18.947  1.00 43.32      B1
ATOM  1371 N   PHE  214    49.242 40.571  20.876  1.00 38.86      B1
ATOM  1372 H   PHE  214    49.414 41.370  21.410  1.00  0.00      B1
ATOM  1373 CA  PHE  214    48.210 39.664  21.336  1.00 37.40      B1
ATOM  1374 CB  PHE  214    47.568 40.064  22.634  1.00 37.45      B1
ATOM  1375 CG  PHE  214    46.494 39.080  23.035  1.00 41.01      B1
ATOM  1376 CD1 PHE  214    45.176 39.459  23.044  1.00 42.77      B1
ATOM  1377 CD2 PHE  214    46.818 37.794  23.400  1.00 42.02      B1
ATOM  1378 CE1 PHE  214    44.197 38.554  23.423  1.00 41.82      B1
ATOM  1379 CE2 PHE  214    45.834 36.898  23.776  1.00 41.70      B1
ATOM  1380 CZ  PHE  214    44.519 37.277  23.791  1.00 41.05      B1
ATOM  1381 C   PHE  214    47.109 39.656  20.321  1.00 36.54      B1
ATOM  1382 O   PHE  214    46.735 38.566  19.889  1.00 37.99      B1
ATOM  1383 N   LEU  215    46.616 40.812  19.893  1.00 33.27      B1
ATOM  1384 H   LEU  215    47.008 41.642  20.238  1.00  0.00      B1
ATOM  1385 CA  LEU  215    45.504 40.864  18.966  1.00 30.38      B1
ATOM  1386 CB  LEU  215    45.099 42.282  18.701  1.00 31.82      B1
ATOM  1387 CG  LEU  215    43.857 42.530  17.893  1.00 32.78      B1
ATOM  1388 CD1 LEU  215    42.727 41.963  18.737  1.00 32.95      B1
ATOM  1389 CD2 LEU  215    43.688 44.011  17.508  1.00 28.93      B1
ATOM  1390 C   LEU  215    45.811 40.232  17.648  1.00 29.57      B1
ATOM  1391 O   LEU  215    44.922 39.632  17.055  1.00 31.28      B1
ATOM  1392 N   LEU  216    47.031 40.379  17.155  1.00 29.44      B1
ATOM  1393 H   LEU  216    47.677 40.935  17.646  1.00  0.00      B1
ATOM  1394 CA  LEU  216    47.465 39.790  15.893  1.00 29.89      B1
ATOM  1395 CB  LEU  216    48.791 40.450  15.472  1.00 28.61      B1
ATOM  1396 CG  LEU  216    48.682 41.877  14.939  1.00 26.83      B1
ATOM  1397 CD1 LEU  216    49.925 42.558  15.344  1.00 28.57      B1
ATOM  1398 CD2 LEU  216    48.446 41.950  13.452  1.00 24.09      B1
ATOM  1399 C   LEU  216    47.613 38.274  16.062  1.00 31.23      B1
ATOM  1400 O   LEU  216    47.328 37.514  15.138  1.00 29.20      B1
ATOM  1401 N   LYS  217    47.999 37.826  17.261  1.00 32.50      B1
ATOM  1402 H   LYS  217    48.305 38.482  17.926  1.00  0.00      B1
ATOM  1403 CA  LYS  217    48.067 36.439  17.599  1.00 34.90      B1
ATOM  1404 CB  LYS  217    48.645 36.280  19.002  1.00 38.07      B1
ATOM  1405 CG  LYS  217    49.394 34.978  19.109  1.00 45.25      B1
ATOM  1406 CD  LYS  217    49.714 34.491  20.521  1.00 53.27      B1
ATOM  1407 CE  LYS  217    50.229 33.024  20.297  1.00 59.03      B1
ATOM  1408 NZ  LYS  217    50.213 32.135  21.467  1.00 62.10      B1
ATOM  1409 HZ1 LYS  217    49.239 32.056  21.824  1.00  0.00      B1
ATOM  1410 HZ2 LYS  217    50.830 32.515  22.214  1.00  0.00      B1
ATOM  1411 HZ3 LYS  217    50.554 31.195  21.179  1.00  0.00      B1
ATOM  1412 C   LYS  217    46.617 35.950  17.546  1.00 36.77      B1
ATOM  1413 O   LYS  217    46.311 34.933  16.886  1.00 39.58      B1
ATOM  1414 N   CYS  218    45.664 36.638  18.177  1.00 34.86      B1
ATOM  1415 H   CYS  218    45.907 37.388  18.751  1.00  0.00      B1
ATOM  1416 CA  CYS  218    44.277 36.238  18.076  1.00 33.61      B1
ATOM  1417 CB  CYS  218    43.430 37.175  18.846  1.00 33.21      B1
ATOM  1418 SG  CYS  218    43.856 36.710  20.515  1.00 35.92      B1
ATOM  1419 C   CYS  218    43.766 36.189  16.652  1.00 32.89      B1
ATOM  1420 O   CYS  218    43.155 35.169  16.323  1.00 34.71      B1
ATOM  1421 N   LEU  219    44.035 37.169  15.777  1.00 29.52      B1
ATOM  1422 H   LEU  219    44.512 37.960  16.104  1.00  0.00      B1
ATOM  1423 CA  LEU  219    43.614 37.119  14.393  1.00 27.44      B1
ATOM  1424 CB  LEU  219    44.116 38.412  13.727  1.00 26.24      B1
ATOM  1425 CG  LEU  219    43.884 38.768  12.241  1.00 25.07      B1
ATOM  1426 CD1 LEU  219    42.402 38.975  11.996  1.00 26.24      B1
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FIGURE 5

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ATOM  1427 CD2 LEU  219      44.563  40.051  11.882  1.00 22.10      B1
ATOM  1428 C   LEU  219      44.121  35.867  13.634  1.00 28.24      B1
ATOM  1429 O   LEU  219      43.373  35.204  12.889  1.00 27.12      B1
ATOM  1430 N   GLU  220      45.399  35.499  13.795  1.00 28.06      B1
ATOM  1431 H   GLU  220      45.957  35.974  14.448  1.00  0.00      B1
ATOM  1432 CA  GLU  220      45.963  34.411  13.048  1.00 28.38      B1
ATOM  1433 CB  GLU  220      47.376  34.198  13.469  1.00 34.25      B1
ATOM  1434 CG  GLU  220      48.049  33.079  12.666  1.00 46.36      B1
ATOM  1435 CD  GLU  220      49.545  32.794  12.907  1.00 55.51      B1
ATOM  1436 OE1 GLU  220      50.113  32.133  12.021  1.00 58.95      B1
ATOM  1437 OE2 GLU  220      50.144  33.213  13.930  1.00 60.41      B1
ATOM  1438 C   GLU  220      45.134  33.193  13.354  1.00 27.30      B1
ATOM  1439 O   GLU  220      44.662  32.524  12.437  1.00 27.08      B1
ATOM  1440 N   GLN  221      44.866  33.023  14.642  1.00 25.42      B1
ATOM  1441 H   GLN  221      45.229  33.687  15.268  1.00  0.00      B1
ATOM  1442 CA  GLN  221      44.074  31.940  15.176  1.00 26.28      B1
ATOM  1443 CB  GLN  221      44.143  31.927  16.691  1.00 26.78      B1
ATOM  1444 CG  GLN  221      45.555  31.456  17.011  1.00 29.19      B1
ATOM  1445 CD  GLN  221      45.752  31.067  18.442  1.00 31.98      B1
ATOM  1446 OE1 GLN  221      46.472  30.162  18.808  1.00 35.98      B1
ATOM  1447 NE2 GLN  221      45.110  31.736  19.347  1.00 39.31      B1
ATOM  1448 HE21 GLN  221      45.263  31.423  20.246  1.00  0.00      B1
ATOM  1449 HE22 GLN  221      44.571  32.514  19.111  1.00  0.00      B1
ATOM  1450 C   GLN  221      42.615  31.925  14.789  1.00 26.21      B1
ATOM  1451 O   GLN  221      42.186  30.896  14.269  1.00 30.69      B1
ATOM  1452 N   VAL  222      41.814  32.962  14.984  1.00 23.63      B1
ATOM  1453 H   VAL  222      42.199  33.746  15.426  1.00  0.00      B1
ATOM  1454 CA  VAL  222      40.429  33.034  14.537  1.00 21.92      B1
ATOM  1455 CB  VAL  222      39.934  34.442  14.793  1.00 21.36      B1
ATOM  1456 CG1 VAL  222      38.706  34.831  14.027  1.00 17.72      B1
ATOM  1457 CG2 VAL  222      39.671  34.496  16.257  1.00 20.95      B1
ATOM  1458 C   VAL  222      40.374  32.707  13.066  1.00 22.65      B1
ATOM  1459 O   VAL  222      39.475  32.013  12.632  1.00 23.72      B1
ATOM  1460 N   ARG  223      41.341  33.120  12.283  1.00 23.95      B1
ATOM  1461 H   ARG  223      42.099  33.614  12.666  1.00  0.00      B1
ATOM  1462 CA  ARG  223      41.309  32.939  10.844  1.00 27.19      B1
ATOM  1463 CB  ARG  223      42.294  33.935  10.283  1.00 29.26      B1
ATOM  1464 CG  ARG  223      42.102  34.364   8.869  1.00 35.23      B1
ATOM  1465 CD  ARG  223      42.880  33.487   7.929  1.00 41.88      B1
ATOM  1466 NE  ARG  223      41.972  32.676   7.096  1.00 47.42      B1
ATOM  1467 HE  ARG  223      41.451  31.953   7.502  1.00  0.00      B1
ATOM  1468 CZ  ARG  223      41.875  32.896   5.784  1.00 46.15      B1
ATOM  1469 NH1 ARG  223      42.575  33.837   5.246  1.00 49.54      B1
ATOM  1470 HH11 ARG  223      42.522  33.989   4.259  1.00  0.00      B1
ATOM  1471 HH12 ARG  223      43.156  34.428   5.805  1.00  0.00      B1
ATOM  1472 NH2 ARG  223      41.178  32.161   4.952  1.00 45.74      B1
ATOM  1473 HH21 ARG  223      40.697  31.353   5.290  1.00  0.00      B1
ATOM  1474 HH22 ARG  223      41.154  32.399   3.980  1.00  0.00      B1
ATOM  1475 C   ARG  223      41.624  31.492  10.430  1.00 29.13      B1
ATOM  1476 O   ARG  223      41.181  30.987   9.376  1.00 29.32      B1
ATOM  1477 N   LYS  224      42.413  30.791  11.259  1.00 29.17      B1
ATOM  1478 H   LYS  224      42.791  31.235  12.048  1.00  0.00      B1
ATOM  1479 CA  LYS  224      42.714  29.411  10.994  1.00 27.70      B1
ATOM  1480 CB  LYS  224      43.922  29.085  11.818  1.00 30.07      B1
ATOM  1481 CG  LYS  224      44.372  27.660  11.706  1.00 36.70      B1
ATOM  1482 CD  LYS  224      45.829  27.544  12.127  1.00 41.68      B1
ATOM  1483 CE  LYS  224      46.303  26.478  11.131  1.00 48.18      B1
ATOM  1484 NZ  LYS  224      47.750  26.492  10.913  1.00 53.57      B1
ATOM  1485 HZ1 LYS  224      48.230  26.241  11.801  1.00  0.00      B1
ATOM  1486 HZ2 LYS  224      48.057  27.436  10.606  1.00  0.00      B1
ATOM  1487 HZ3 LYS  224      47.998  25.792  10.183  1.00  0.00      B1
ATOM  1488 C   LYS  224      41.464  28.598  11.347  1.00 26.27      B1
ATOM  1489 O   LYS  224      40.970  27.810  10.510  1.00 24.82      B1
ATOM  1490 N   ILE  225      40.892  28.835  12.547  1.00 24.75      B1
ATOM  1491 H   ILE  225      41.308  29.487  13.151  1.00  0.00      B1
ATOM  1492 CA  ILE  225      39.656  28.147  12.943  1.00 23.33      B1
ATOM  1493 CB  ILE  225      39.146  28.622  14.296  1.00 18.08      B1
ATOM  1494 CG2 ILE  225      37.874  27.872  14.577  1.00 15.43      B1
ATOM  1495 CG1 ILE  225      40.161  28.400  15.380  1.00 13.38      B1
ATOM  1496 CD  ILE  225      39.787  28.967  16.749  1.00 13.59      B1
ATOM  1497 C   ILE  225      38.594  28.437  11.889  1.00 27.28      B1
ATOM  1498 O   ILE  225      37.978  27.492  11.400  1.00 31.49      B1
ATOM  1499 N   GLN  226      38.396  29.677  11.402  1.00 29.69      B1
ATOM  1500 H   GLN  226      38.894  30.413  11.803  1.00  0.00      B1
ATOM  1501 CA  GLN  226      37.450  29.969  10.313  1.00 29.12      B1
ATOM  1502 CB  GLN  226      37.366  31.438   9.962  1.00 32.26      B1
ATOM  1503 CG  GLN  226      36.682  32.156  11.108  1.00 36.28      B1
ATOM  1504 CD  GLN  226      36.429  33.613  10.816  1.00 37.88      B1
ATOM  1505 OE1 GLN  226      37.158  34.281  10.076  1.00 36.34      B1
ATOM  1506 NE2 GLN  226      35.359  34.114  11.421  1.00 39.62      B1
ATOM  1507 HE21 GLN  226      34.823  33.501  11.971  1.00  0.00      B1
ATOM  1508 HE22 GLN  226      35.153  35.057  11.287  1.00  0.00      B1
ATOM  1509 C   GLN  226      37.714  29.295   9.007  1.00 26.82      B1
ATOM  1510 O   GLN  226      36.775  28.887   8.325  1.00 27.45      B1
ATOM  1511 N   GLY  227      38.940  29.186   8.570  1.00 26.55      B1
ATOM  1512 H   GLY  227      39.688  29.612   9.043  1.00  0.00      B1
ATOM  1513 CA  GLY  227      39.195  28.427   7.348  1.00 27.27      B1
ATOM  1514 C   GLY  227      38.832  26.949   7.574  1.00 27.65      B1
ATOM  1515 O   GLY  227      38.287  26.291   6.656  1.00 26.79      B1
ATOM  1516 N   ASP  228      39.025  26.429   8.819  1.00 27.03      B1
ATOM  1517 H   ASP  228      39.460  26.957   9.523  1.00  0.00      B1
ATOM  1518 CA  ASP  228      38.618  25.038   9.052  1.00 28.20      B1
ATOM  1519 CB  ASP  228      38.986  24.492  10.391  1.00 26.04      B1
ATOM  1520 CG  ASP  228      40.427  24.554  10.774  1.00 24.88      B1
ATOM  1521 OD1 ASP  228      40.627  24.521  11.977  1.00 23.37      B1
ATOM  1522 OD2 ASP  228      41.302  24.637   9.912  1.00 23.32      B1
ATOM  1523 C   ASP  228      37.120  24.830   8.992  1.00 27.23      B1
ATOM  1524 O   ASP  228      36.662  23.900   8.336  1.00 27.07      B1
ATOM  1525 N   GLY  229      36.390  25.739   9.639  1.00 26.74      B1
ATOM  1526 H   GLY  229      36.861  26.444  10.134  1.00  0.00      B1
ATOM  1527 CA  GLY  229      34.946  25.723   9.673  1.00 25.87      B1
ATOM  1528 C   GLY  229      34.393  25.825   8.274  1.00 24.95      B1
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FIGURE 5

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ATOM  1631  N   LYS  241      24.174  18.011   0.694  1.00 37.36      B1
ATOM  1632  H   LYS  241      25.091  18.023   0.345  1.00  0.00      B1
ATOM  1633  CA  LYS  241      23.314  19.115   0.275  1.00 36.37      B1
ATOM  1634  CB  LYS  241      22.173  18.648  -0.595  1.00 38.38      B1
ATOM  1635  CG  LYS  241      22.645  17.940  -1.838  1.00 42.94      B1
ATOM  1636  CD  LYS  241      23.468  18.809  -2.737  1.00 46.97      B1
ATOM  1637  CE  LYS  241      23.657  18.070  -4.051  1.00 49.20      B1
ATOM  1638  NZ  LYS  241      22.509  18.372  -4.893  1.00 51.54      B1
ATOM  1639  HZ1 LYS  241      22.447  19.400  -5.038  1.00  0.00      B1
ATOM  1640  HZ2 LYS  241      21.641  18.041  -4.426  1.00  0.00      B1
ATOM  1641  HZ3 LYS  241      22.609  17.895  -5.811  1.00  0.00      B1
ATOM  1642  C   LYS  241      22.720  19.904   1.429  1.00 33.37      B1
ATOM  1643  O   LYS  241      21.728  20.580   1.223  1.00 33.90      B1
ATOM  1644  N   LEU  242      23.286  19.853   2.648  1.00 31.40      B1
ATOM  1645  H   LEU  242      24.055  19.260   2.756  1.00  0.00      B1
ATOM  1646  CA  LEU  242      22.904  20.682   3.758  1.00 31.09      B1
ATOM  1647  CB  LEU  242      23.253  20.059   5.096  1.00 28.55      B1
ATOM  1648  CG  LEU  242      22.571  18.798   5.641  1.00 30.36      B1
ATOM  1649  CD1 LEU  242      22.530  18.814   7.138  1.00 29.62      B1
ATOM  1650  CD2 LEU  242      21.086  18.861   5.443  1.00 31.94      B1
ATOM  1651  C   LEU  242      23.778  21.933   3.550  1.00 34.03      B1
ATOM  1652  O   LEU  242      24.903  22.027   4.058  1.00 35.53      B1
ATOM  1653  N   CYS  243      23.316  22.883   2.722  1.00 34.89      B1
ATOM  1654  H   CYS  243      22.491  22.665   2.238  1.00  0.00      B1
ATOM  1655  CA  CYS  243      24.051  24.083   2.377  1.00 35.42      B1
ATOM  1656  C   CYS  243      23.492  25.335   2.975  1.00 36.85      B1
ATOM  1657  O   CYS  243      23.956  26.400   2.565  1.00 40.10      B1
ATOM  1658  CB  CYS  243      24.046  24.383   0.929  1.00 33.12      B1
ATOM  1659  SG  CYS  243      24.438  22.883   0.099  1.00 38.25      B1
ATOM  1660  N   HIS  244      22.496  25.393   3.848  1.00 35.37      B1
ATOM  1661  H   HIS  244      22.185  24.588   4.318  1.00  0.00      B1
ATOM  1662  CA  HIS  244      21.939  26.676   4.191  1.00 33.29      B1
ATOM  1663  CB  HIS  244      20.655  26.987   3.340  1.00 33.64      B1
ATOM  1664  CG  HIS  244      20.915  27.205   1.857  1.00 33.12      B1
ATOM  1665  CD2 HIS  244      20.288  26.584   0.814  1.00 37.29      B1
ATOM  1666  ND1 HIS  244      21.874  27.902   1.298  1.00 36.85      B1
ATOM  1667  HD1 HIS  244      22.648  28.281   1.778  1.00  0.00      B1
ATOM  1668  CE1 HIS  244      21.874  27.722  -0.013  1.00 35.95      B1
ATOM  1669  NE2 HIS  244      20.910  26.920  -0.301  1.00 35.54      B1
ATOM  1670  HE2 HIS  244      20.616  26.706  -1.214  1.00  0.00      B1
ATOM  1671  C   HIS  244      21.621  26.565   5.650  1.00 33.38      B1
ATOM  1672  O   HIS  244      20.546  26.105   6.029  1.00 33.23      B1
ATOM  1673  N   PRO  245      22.539  27.018   6.499  1.00 33.21      B1
ATOM  1674  CD  PRO  245      23.851  27.524   6.099  1.00 31.29      B1
ATOM  1675  CA  PRO  245      22.373  26.979   7.948  1.00 34.16      B1
ATOM  1676  CB  PRO  245      23.490  27.799   8.467  1.00 32.85      B1
ATOM  1677  CG  PRO  245      24.564  27.549   7.428  1.00 31.74      B1
ATOM  1678  C   PRO  245      21.032  27.470   8.407  1.00 36.26      B1
ATOM  1679  O   PRO  245      20.478  26.878   9.315  1.00 38.13      B1
ATOM  1680  N   GLU  246      20.529  28.463   7.640  1.00 39.64      B1
ATOM  1681  H   GLU  246      21.134  28.747   6.934  1.00  0.00      B1
ATOM  1682  CA  GLU  246      19.257  29.229   7.711  1.00 41.10      B1
ATOM  1683  CB  GLU  246      19.044  30.107   6.438  1.00 44.15      B1
ATOM  1684  CG  GLU  246      20.256  30.918   5.944  1.00 47.07      B1
ATOM  1685  CD  GLU  246      20.813  30.539   4.558  1.00 52.53      B1
ATOM  1686  OE1 GLU  246      22.054  30.545   4.374  1.00 54.22      B1
ATOM  1687  OE2 GLU  246      20.002  30.250   3.656  1.00 54.39      B1
ATOM  1688  C   GLU  246      18.071  28.298   7.819  1.00 40.57      B1
ATOM  1689  O   GLU  246      17.308  28.338   8.791  1.00 39.90      B1
ATOM  1690  N   GLU  247      19.025  27.388   6.840  1.00 40.32      B1
ATOM  1691  H   GLU  247      18.750  27.334   6.190  1.00  0.00      B1
ATOM  1692  CA  GLU  247      17.001  26.347   6.830  1.00 40.76      B1
ATOM  1693  CB  GLU  247      17.139  25.423   5.642  1.00 44.05      B1
ATOM  1694  CG  GLU  247      16.830  26.240   4.400  1.00 48.54      B1
ATOM  1695  CD  GLU  247      17.163  25.628   3.050  1.00 50.24      B1
ATOM  1696  OE1 GLU  247      16.849  26.299   2.056  1.00 52.92      B1
ATOM  1697  OE2 GLU  247      17.744  24.533   2.987  1.00 50.84      B1
ATOM  1698  C   GLU  247      16.966  25.444   8.034  1.00 39.24      B1
ATOM  1699  O   GLU  247      15.915  24.888   8.329  1.00 39.40      B1
ATOM  1700  N   LEU  248      18.066  25.280   8.760  1.00 37.92      B1
ATOM  1701  H   LEU  248      18.864  25.814   8.576  1.00  0.00      B1
ATOM  1702  CA  LEU  248      18.101  24.338   9.858  1.00 35.75      B1
ATOM  1703  CB  LEU  248      19.458  23.623   9.796  1.00 34.18      B1
ATOM  1704  CG  LEU  248      19.669  22.866   8.430  1.00 34.00      B1
ATOM  1705  CD1 LEU  248      20.997  22.149   8.306  1.00 33.97      B1
ATOM  1706  CD2 LEU  248      18.620  21.810   8.322  1.00 32.33      B1
ATOM  1707  C   LEU  248      17.871  25.031  11.153  1.00 36.51      B1
ATOM  1708  O   LEU  248      17.736  24.370  12.186  1.00 36.31      B1
ATOM  1709  N   VAL  249      17.663  26.350  11.146  1.00 36.88      B1
ATOM  1710  H   VAL  249      17.566  26.810  10.283  1.00  0.00      B1
ATOM  1711  CA  VAL  249      17.573  27.133  12.371  1.00 41.39      B1
ATOM  1712  CB  VAL  249      17.265  28.640  12.020  1.00 43.72      B1
ATOM  1713  CG1 VAL  249      15.804  28.985  11.776  1.00 44.70      B1
ATOM  1714  CG2 VAL  249      17.702  29.434  13.214  1.00 45.20      B1
ATOM  1715  C   VAL  249      16.590  26.635  13.406  1.00 42.61      B1
ATOM  1716  O   VAL  249      16.912  26.716  14.594  1.00 44.77      B1
ATOM  1717  N   LEU  250      15.453  26.035  13.016  1.00 43.61      B1
ATOM  1718  H   LEU  250      15.319  25.919  12.053  1.00  0.00      B1
ATOM  1719  CA  LEU  250      14.457  25.537  13.987  1.00 44.96      B1
ATOM  1720  CB  LEU  250      13.102  25.296  13.373  1.00 44.88      B1
ATOM  1721  CG  LEU  250      12.729  26.281  12.313  1.00 47.04      B1
ATOM  1722  CD1 LEU  250      13.092  25.577  11.011  1.00 47.40      B1
ATOM  1723  CD2 LEU  250      11.286  26.772  12.441  1.00 46.18      B1
ATOM  1724  C   LEU  250      14.852  24.207  14.626  1.00 43.96      B1
ATOM  1725  O   LEU  250      14.450  23.887  15.764  1.00 44.07      B1
ATOM  1726  N   LEU  251      15.691  23.446  13.893  1.00 42.41      B1
ATOM  1727  H   LEU  251      16.049  23.788  13.048  1.00  0.00      B1
ATOM  1728  CA  LEU  251      16.155  22.159  14.362  1.00 40.63      B1
ATOM  1729  CB  LEU  251      16.834  21.418  13.257  1.00 36.37      B1
ATOM  1730  CG  LEU  251      15.996  20.629  12.267  1.00 33.26      B1
ATOM  1731  CD1 LEU  251      14.595  21.168  11.956  1.00 33.46      B1
ATOM  1732  CD2 LEU  251      16.875  20.619  11.050  1.00 34.71      B1
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FIGURE 5

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ATOM  1529 O   GLY  229      33.370  25.222   7.956  1.00 25.73      B1
ATOM  1530 N   ALA  230      35.058  26.541   7.391  1.00 23.97      B1
ATOM  1531 H   ALA  230      35.871  27.026   7.654  1.00  0.00      B1
ATOM  1532 CA  ALA  230      34.530  26.688   6.061  1.00 25.94      B1
ATOM  1533 CB  ALA  230      35.193  27.852   5.312  1.00 19.76      B1
ATOM  1534 C   ALA  230      34.794  25.403   5.304  1.00 29.42      B1
ATOM  1535 O   ALA  230      34.014  25.061   4.423  1.00 32.07      B1
ATOM  1536 N   ALA  231      35.878  24.671   5.572  1.00 32.16      B1
ATOM  1537 H   ALA  231      36.556  25.045   6.175  1.00  0.00      B1
ATOM  1538 CA  ALA  231      36.141  23.364   4.957  1.00 31.99      B1
ATOM  1539 CB  ALA  231      37.489  22.847   5.428  1.00 32.77      B1
ATOM  1540 C   ALA  231      35.060  22.361   5.386  1.00 32.99      B1
ATOM  1541 O   ALA  231      34.599  21.575   4.576  1.00 34.12      B1
ATOM  1542 N   LEU  232      34.662  22.309   6.652  1.00 33.30      B1
ATOM  1543 H   LEU  232      35.174  22.861   7.284  1.00  0.00      B1
ATOM  1544 CA  LEU  232      33.558  21.506   7.165  1.00 35.33      B1
ATOM  1545 CB  LEU  232      33.279  21.783   8.626  1.00 34.22      B1
ATOM  1546 CG  LEU  232      32.410  20.861   9.394  1.00 33.16      B1
ATOM  1547 CD1 LEU  232      33.191  19.545   9.451  1.00 34.59      B1
ATOM  1548 CD2 LEU  232      32.107  21.381  10.800  1.00 31.32      B1
ATOM  1549 C   LEU  232      32.271  21.829   6.440  1.00 36.65      B1
ATOM  1550 O   LEU  232      31.703  20.986   5.749  1.00 36.42      B1
ATOM  1551 N   GLN  233      31.836  23.084   6.570  1.00 38.89      B1
ATOM  1552 H   GLN  233      32.378  23.719   7.087  1.00  0.00      B1
ATOM  1553 CA  GLN  233      30.637  23.579   5.933  1.00 40.02      B1
ATOM  1554 CB  GLN  233      30.572  25.072   6.162  1.00 42.25      B1
ATOM  1555 CG  GLN  233      30.290  25.398   7.626  1.00 48.22      B1
ATOM  1556 CD  GLN  233      30.021  26.879   7.983  1.00 53.75      B1
ATOM  1557 OE1 GLN  233      30.799  27.810   7.718  1.00 55.93      B1
ATOM  1558 NE2 GLN  233      28.909  27.215   8.634  1.00 56.51      B1
ATOM  1559 HE21 GLN  233      28.810  28.144   8.902  1.00  0.00      B1
ATOM  1560 HE22 GLN  233      28.205  26.533   8.710  1.00  0.00      B1
ATOM  1561 C   GLN  233      30.635  23.243   4.441  1.00 39.70      B1
ATOM  1562 O   GLN  233      29.631  22.777   3.898  1.00 40.20      B1
ATOM  1563 N   GLU  234      31.744  23.377   3.736  1.00 39.32      B1
ATOM  1564 H   GLU  234      32.544  23.750   4.163  1.00  0.00      B1
ATOM  1565 CA  GLU  234      31.809  23.025   2.329  1.00 39.23      B1
ATOM  1566 CB  GLU  234      33.155  23.434   1.811  1.00 40.25      B1
ATOM  1567 CG  GLU  234      33.292  23.028   0.383  1.00 47.69      B1
ATOM  1568 CD  GLU  234      34.733  23.056  -0.073  1.00 53.40      B1
ATOM  1569 OE1 GLU  234      34.986  23.721  -1.100  1.00 53.78      B1
ATOM  1570 OE2 GLU  234      35.568  22.400   0.590  1.00 57.55      B1
ATOM  1571 C   GLU  234      31.580  21.535   2.136  1.00 37.09      B1
ATOM  1572 O   GLU  234      30.884  21.217   1.188  1.00 36.67      B1
ATOM  1573 N   LYS  235      32.092  20.623   2.986  1.00 37.27      B1
ATOM  1574 H   LYS  235      32.668  20.965   3.706  1.00  0.00      B1
ATOM  1575 CA  LYS  235      31.832  19.177   2.942  1.00 36.27      B1
ATOM  1576 CB  LYS  235      32.516  18.365   3.997  1.00 34.92      B1
ATOM  1577 CG  LYS  235      33.978  18.483   4.107  1.00 38.47      B1
ATOM  1578 CD  LYS  235      34.762  17.999   2.921  1.00 38.07      B1
ATOM  1579 CE  LYS  235      36.192  18.051   3.460  1.00 39.15      B1
ATOM  1580 NZ  LYS  235      37.117  17.460   2.521  1.00 41.34      B1
ATOM  1581 HZ1 LYS  235      37.080  17.978   1.622  1.00  0.00      B1
ATOM  1582 HZ2 LYS  235      36.854  16.466   2.363  1.00  0.00      B1
ATOM  1583 HZ3 LYS  235      38.080  17.497   2.911  1.00  0.00      B1
ATOM  1584 C   LYS  235      30.363  18.847   3.204  1.00 35.20      B1
ATOM  1585 O   LYS  235      29.722  18.102   2.463  1.00 35.60      B1
ATOM  1586 N   LEU  236      29.807  19.332   4.301  1.00 33.58      B1
ATOM  1587 H   LEU  236      30.363  19.888   4.885  1.00  0.00      B1
ATOM  1588 CA  LEU  236      28.417  19.116   4.641  1.00 32.40      B1
ATOM  1589 CB  LEU  236      28.093  19.918   5.894  1.00 28.65      B1
ATOM  1590 CG  LEU  236      28.791  19.441   7.148  1.00 28.23      B1
ATOM  1591 CD1 LEU  236      28.703  20.460   8.268  1.00 24.14      B1
ATOM  1592 CD2 LEU  236      28.132  18.163   7.587  1.00 26.66      B1
ATOM  1593 C   LEU  236      27.590  19.574   3.453  1.00 33.69      B1
ATOM  1594 O   LEU  236      26.691  18.849   3.064  1.00 35.13      B1
ATOM  1595 N   CYS  237      27.870  20.670   2.753  1.00 34.49      B1
ATOM  1596 H   CYS  237      28.611  21.251   3.025  1.00  0.00      B1
ATOM  1597 CA  CYS  237      27.064  21.016   1.606  1.00 34.95      B1
ATOM  1598 C   CYS  237      27.324  20.090   0.451  1.00 35.97      B1
ATOM  1599 O   CYS  237      26.360  19.573  -0.089  1.00 36.09      B1
ATOM  1600 CB  CYS  237      27.334  22.413   1.130  1.00 35.18      B1
ATOM  1601 SG  CYS  237      26.409  22.880  -0.365  1.00 36.40      B1
ATOM  1602 N   ALA  238      28.571  19.804   0.074  1.00 37.29      B1
ATOM  1603 H   ALA  238      29.324  20.158   0.591  1.00  0.00      B1
ATOM  1604 CA  ALA  238      28.841  18.973  -1.090  1.00 36.80      B1
ATOM  1605 CB  ALA  238      30.274  18.684  -1.403  1.00 37.35      B1
ATOM  1606 C   ALA  238      28.320  17.617  -0.911  1.00 36.49      B1
ATOM  1607 O   ALA  238      27.645  17.198  -1.809  1.00 36.54      B1
ATOM  1608 N   THR  239      28.628  16.969   0.193  1.00 38.80      B1
ATOM  1609 H   THR  239      29.236  17.391   0.821  1.00  0.00      B1
ATOM  1610 CA  THR  239      28.230  15.587   0.464  1.00 41.31      B1
ATOM  1611 CB  THR  239      29.158  15.035   1.554  1.00 42.38      B1
ATOM  1612 OG1 THR  239      30.473  15.265   1.031  1.00 45.70      B1
ATOM  1613 HG1 THR  239      31.019  15.668   1.709  1.00  0.00      B1
ATOM  1614 CG2 THR  239      28.936  13.574   1.916  1.00 41.85      B1
ATOM  1615 C   THR  239      26.771  15.341   0.864  1.00 41.94      B1
ATOM  1616 O   THR  239      26.260  14.284   0.460  1.00 43.34      B1
ATOM  1617 N   TYR  240      26.095  16.207   1.669  1.00 40.07      B1
ATOM  1618 H   TYR  240      26.538  17.034   1.953  1.00  0.00      B1
ATOM  1619 CA  TYR  240      24.718  15.992   2.084  1.00 38.21      B1
ATOM  1620 CB  TYR  240      24.594  15.993   3.618  1.00 38.08      B1
ATOM  1621 CG  TYR  240      25.524  14.926   4.193  1.00 43.37      B1
ATOM  1622 CD1 TYR  240      26.475  15.243   5.149  1.00 45.06      B1
ATOM  1623 CE1 TYR  240      27.420  14.283   5.529  1.00 47.35      B1
ATOM  1624 CD2 TYR  240      25.518  13.643   3.641  1.00 43.89      B1
ATOM  1625 CE2 TYR  240      26.442  12.690   4.003  1.00 44.77      B1
ATOM  1626 CZ  TYR  240      27.410  13.005   4.943  1.00 47.96      B1
ATOM  1627 OH  TYR  240      28.390  12.047   5.244  1.00 46.59      B1
ATOM  1628 HH  TYR  240      28.027  11.187   4.992  1.00  0.00      B1
ATOM  1629 C   TYR  240      23.781  17.032   1.516  1.00 39.49      B1
ATOM  1630 O   TYR  240      22.587  16.934   1.775  1.00 42.76      B1
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FIGURE 5

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ATOM  1733 C   LEU  251     17.104  22.372  15.493  1.00 42.78      B1
ATOM  1734 O   LEU  251     17.124  21.554  16.395  1.00 45.44      B1
ATOM  1735 N   GLY  252     17.826  23.477  15.610  1.00 44.86      B1
ATOM  1736 H   GLY  252     17.750  24.160  14.910  1.00  0.00      B1
ATOM  1737 CA  GLY  252     18.734  23.711  16.719  1.00 46.68      B1
ATOM  1738 C   GLY  252     18.071  23.596  18.067  1.00 49.18      B1
ATOM  1739 O   GLY  252     18.709  23.318  19.077  1.00 49.23      B1
ATOM  1740 N   HIS  253     16.756  23.787  18.046  1.00 53.74      B1
ATOM  1741 H   HIS  253     16.358  24.055  17.190  1.00  0.00      B1
ATOM  1742 CA  HIS  253     15.859  23.649  19.197  1.00 57.46      B1
ATOM  1743 CB  HIS  253     14.468  24.157  18.764  1.00 62.93      B1
ATOM  1744 CG  HIS  253     13.212  23.813  19.577  1.00 68.75      B1
ATOM  1745 CD2 HIS  253     12.031  24.529  19.414  1.00 71.00      B1
ATOM  1746 ND1 HIS  253     12.980  22.854  20.479  1.00 70.67      B1
ATOM  1747 HD1 HIS  253     13.627  22.193  20.830  1.00  0.00      B1
ATOM  1748 CE1 HIS  253     11.723  22.966  20.845  1.00 73.40      B1
ATOM  1749 NE2 HIS  253     11.156  23.973  20.204  1.00 72.91      B1
ATOM  1750 HE2 HIS  253     10.218  24.260  20.311  1.00  0.00      B1
ATOM  1751 C   HIS  253     15.771  22.209  19.691  1.00 56.06      B1
ATOM  1752 O   HIS  253     15.880  21.827  20.857  1.00 56.17      B1
ATOM  1753 N   SER  254     15.395  21.435  18.724  1.00 53.46      B1
ATOM  1754 H   SER  254     15.278  21.783  17.813  1.00  0.00      B1
ATOM  1755 CA  SER  254     15.177  20.034  18.898  1.00 52.61      B1
ATOM  1756 CB  SER  254     14.613  19.595  17.576  1.00 53.04      B1
ATOM  1757 OG  SER  254     13.793  20.686  17.158  1.00 56.04      B1
ATOM  1758 HG  SER  254     13.369  20.467  16.319  1.00  0.00      B1
ATOM  1759 C   SER  254     16.512  19.386  19.275  1.00 51.48      B1
ATOM  1760 O   SER  254     16.596  18.639  20.245  1.00 51.90      B1
ATOM  1761 N   LEU  255     17.577  19.790  18.562  1.00 49.31      B1
ATOM  1762 H   LEU  255     17.430  20.480  17.889  1.00  0.00      B1
ATOM  1763 CA  LEU  255     18.913  19.272  18.723  1.00 46.02      B1
ATOM  1764 CB  LEU  255     19.706  19.723  17.537  1.00 44.66      B1
ATOM  1765 CG  LEU  255     19.362  18.968  16.274  1.00 44.51      B1
ATOM  1766 CD1 LEU  255     19.810  19.679  15.006  1.00 43.16      B1
ATOM  1767 CD2 LEU  255     19.969  17.604  16.456  1.00 44.67      B1
ATOM  1768 C   LEU  255     19.536  19.718  20.012  1.00 46.56      B1
ATOM  1769 O   LEU  255     20.565  19.174  20.440  1.00 46.82      B1
ATOM  1770 N   GLY  256     18.918  20.759  20.581  1.00 45.93      B1
ATOM  1771 H   GLY  256     18.210  21.225  20.101  1.00  0.00      B1
ATOM  1772 CA  GLY  256     19.277  21.273  21.890  1.00 46.68      B1
ATOM  1773 C   GLY  256     20.669  21.866  21.970  1.00 47.28      B1
ATOM  1774 O   GLY  256     21.273  21.844  23.056  1.00 49.64      B1
ATOM  1775 N   ILE  257     21.143  22.441  20.849  1.00 45.74      B1
ATOM  1776 H   ILE  257     20.497  22.589  20.128  1.00  0.00      B1
ATOM  1777 CA  ILE  257     22.481  23.017  20.726  1.00 43.64      B1
ATOM  1778 CB  ILE  257     22.684  23.363  19.257  1.00 42.54      B1
ATOM  1779 CG2 ILE  257     23.988  24.110  19.073  1.00 41.05      B1
ATOM  1780 CG1 ILE  257     22.694  22.088  18.437  1.00 40.55      B1
ATOM  1781 CD  ILE  257     22.452  22.468  16.970  1.00 39.49      B1
ATOM  1782 C   ILE  257     22.559  24.246  21.616  1.00 43.27      B1
ATOM  1783 O   ILE  257     21.706  25.110  21.450  1.00 43.22      B1
ATOM  1784 N   PRO  258     23.441  24.392  22.608  1.00 43.05      B1
ATOM  1785 CD  PRO  258     24.133  23.321  23.296  1.00 43.29      B1
ATOM  1786 CA  PRO  258     23.559  25.616  23.360  1.00 43.82      B1
ATOM  1787 CB  PRO  258     24.295  25.236  24.612  1.00 41.97      B1
ATOM  1788 CG  PRO  258     25.107  24.064  24.186  1.00 43.79      B1
ATOM  1789 C   PRO  258     24.252  26.703  22.555  1.00 46.06      B1
ATOM  1790 O   PRO  258     24.983  26.513  21.560  1.00 46.59      B1
ATOM  1791 N   TRP  259     23.996  27.887  23.106  1.00 46.75      B1
ATOM  1792 H   TRP  259     23.588  27.921  23.994  1.00  0.00      B1
ATOM  1793 CA  TRP  259     24.427  29.143  22.517  1.00 45.77      B1
ATOM  1794 CB  TRP  259     23.213  30.071  22.397  1.00 46.60      B1
ATOM  1795 CG  TRP  259     23.556  31.372  21.749  1.00 47.51      B1
ATOM  1796 CD2 TRP  259     23.860  31.525  20.430  1.00 47.83      B1
ATOM  1797 CE2 TRP  259     24.154  32.888  20.392  1.00 48.47      B1
ATOM  1798 CE3 TRP  259     23.940  30.745  19.290  1.00 47.39      B1
ATOM  1799 CD1 TRP  259     23.639  32.520  22.493  1.00 48.60      B1
ATOM  1800 NE1 TRP  259     24.013  33.421  21.628  1.00 48.27      B1
ATOM  1801 HE1 TRP  259     24.224  34.344  21.870  1.00  0.00      B1
ATOM  1802 CZ2 TRP  259     24.531  33.486  19.195  1.00 47.40      B1
ATOM  1803 CZ3 TRP  259     24.317  31.344  18.097  1.00 49.07      B1
ATOM  1804 CH2 TRP  259     24.613  32.706  18.050  1.00 49.12      B1
ATOM  1805 C   TRP  259     25.459  29.727  23.440  1.00 44.01      B1
ATOM  1806 O   TRP  259     25.340  29.664  24.671  1.00 43.25      B1
ATOM  1807 N   ALA  260     26.469  30.247  22.777  1.00 43.01      B1
ATOM  1808 H   ALA  260     26.523  30.198  21.796  1.00  0.00      B1
ATOM  1809 CA  ALA  260     27.493  30.973  23.482  1.00 43.48      B1
ATOM  1810 CB  ALA  260     28.874  30.549  22.969  1.00 43.33      B1
ATOM  1811 C   ALA  260     27.249  32.486  23.216  1.00 43.41      B1
ATOM  1812 O   ALA  260     27.315  32.946  22.054  1.00 40.55      B1
ATOM  1813 N   PRO  261     26.853  33.267  24.253  1.00 42.61      B1
ATOM  1814 CD  PRO  261     26.527  32.807  25.606  1.00 42.33      B1
ATOM  1815 CA  PRO  261     26.720  34.701  24.199  1.00 42.37      B1
ATOM  1816 CB  PRO  261     25.778  34.987  25.335  1.00 41.46      B1
ATOM  1817 CG  PRO  261     26.251  34.060  26.411  1.00 40.00      B1
ATOM  1818 C   PRO  261     28.087  35.369  24.311  1.00 42.22      B1
ATOM  1819 O   PRO  261     28.988  34.956  25.037  1.00 38.82      B1
ATOM  1820 N   LEU  262     28.234  36.403  23.486  1.00 45.20      B1
ATOM  1821 H   LEU  262     27.513  36.610  22.853  1.00  0.00      B1
ATOM  1822 CA  LEU  262     29.434  37.210  23.498  1.00 46.50      B1
ATOM  1823 CB  LEU  262     30.531  36.609  22.610  1.00 45.09      B1
ATOM  1824 CG  LEU  262     31.903  37.157  22.964  1.00 42.55      B1
ATOM  1825 CD1 LEU  262     32.344  36.695  24.338  1.00 41.52      B1
ATOM  1826 CD2 LEU  262     32.850  36.730  21.900  1.00 44.21      B1
ATOM  1827 C   LEU  262     29.154  38.628  23.035  1.00 48.56      B1
ATOM  1828 O   LEU  262     29.633  39.470  23.790  1.00 48.23      B1
ATOM  1829 N   SER  263     28.388  38.956  21.960  1.00 51.33      B1
ATOM  1830 H   SER  263     27.982  38.242  21.427  1.00  0.00      B1
ATOM  1831 CA  SER  263     28.127  40.339  21.494  1.00 55.19      B1
ATOM  1832 CB  SER  263     26.871  40.511  20.612  1.00 57.17      B1
ATOM  1833 OG  SER  263     26.498  39.411  19.776  1.00 64.12      B1
ATOM  1834 HG  SER  263     26.093  38.741  20.336  1.00  0.00      B1
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FIGURE 5

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ATOM  1835 C   SER  263     27.909  41.354  22.600  1.00 56.15      B1
ATOM  1836 O   SER  263     28.744  42.243  22.753  1.00 57.88      B1
ATOM  1837 N   SER  264     26.899  41.231  23.452  1.00 56.52      B1
ATOM  1838 H   SER  264     26.277  40.478  23.415  1.00  0.00      B1
ATOM  1839 CA  SER  264     26.716  42.204  24.494  1.00 58.28      B1
ATOM  1840 CB  SER  264     25.313  41.977  25.064  1.00 58.77      B1
ATOM  1841 OG  SER  264     25.099  40.726  25.713  1.00 58.50      B1
ATOM  1842 HG  SER  264     25.385  40.832  26.632  1.00  0.00      B1
ATOM  1843 C   SER  264     27.800  42.168  25.584  1.00 59.95      B1
ATOM  1844 O   SER  264     27.610  42.805  26.620  1.00 60.44      B1
ATOM  1845 N   CYS  265     28.948  41.484  25.466  1.00 61.37      B1
ATOM  1846 H   CYS  265     29.192  41.114  24.596  1.00  0.00      B1
ATOM  1847 CA  CYS  265     29.958  41.502  26.509  1.00 62.57      B1
ATOM  1848 CB  CYS  265     30.991  40.418  26.285  1.00 64.32      B1
ATOM  1849 SG  CYS  265     32.322  40.638  27.504  1.00 71.40      B1
ATOM  1850 C   CYS  265     30.667  42.860  26.515  1.00 63.12      B1
ATOM  1851 OT1 CYS  265     31.065  43.360  25.444  1.00 63.44      B1
ATOM  1852 OT2 CYS  265     30.809  43.408  27.610  1.00 61.72      B1
ATOM  1853 CB  ALA  272     40.020  43.327  30.788  1.00 77.44      B2
ATOM  1854 C   ALA  272     38.698  41.201  30.601  1.00 76.53      B2
ATOM  1855 O   ALA  272     37.525  40.873  30.361  1.00 76.81      B2
ATOM  1856 HT1 ALA  272     37.486  43.550  30.261  1.00  0.00      B2
ATOM  1857 HT2 ALA  272     37.357  42.450  28.996  1.00  0.00      B2
ATOM  1858 N   ALA  272     37.973  43.169  29.427  1.00 76.81      B2
ATOM  1859 HT3 ALA  272     38.195  43.924  28.752  1.00  0.00      B2
ATOM  1860 CA  ALA  272     39.176  42.460  29.853  1.00 77.02      B2
ATOM  1861 N   ALA  273     39.485  40.547  31.487  1.00 74.93      B2
ATOM  1862 H   ALA  273     40.334  40.963  31.745  1.00  0.00      B2
ATOM  1863 CA  ALA  273     39.244  39.241  32.119  1.00 72.64      B2
ATOM  1864 CB  ALA  273     39.704  39.279  33.558  1.00 71.92      B2
ATOM  1865 C   ALA  273     37.872  38.599  32.118  1.00 71.60      B2
ATOM  1866 O   ALA  273     37.806  37.458  31.702  1.00 71.68      B2
ATOM  1867 N   GLY  274     36.775  39.282  32.484  1.00 70.20      B2
ATOM  1868 H   GLY  274     36.903  40.167  32.874  1.00  0.00      B2
ATOM  1869 CA  GLY  274     35.412  38.758  32.425  1.00 66.78      B2
ATOM  1870 C   GLY  274     35.050  38.437  30.990  1.00 65.05      B2
ATOM  1871 O   GLY  274     34.627  37.320  30.709  1.00 66.44      B2
ATOM  1872 N   CYS  275     35.301  39.364  30.048  1.00 62.77      B2
ATOM  1873 H   CYS  275     35.634  40.223  30.357  1.00  0.00      B2
ATOM  1874 CA  CYS  275     35.026  39.188  28.611  1.00 59.30      B2
ATOM  1875 C   CYS  275     35.875  38.063  28.054  1.00 55.89      B2
ATOM  1876 O   CYS  275     35.425  37.152  27.351  1.00 54.41      B2
ATOM  1877 CB  CYS  275     35.349  40.466  27.827  1.00 61.50      B2
ATOM  1878 SG  CYS  275     34.119  40.937  26.577  1.00 66.63      B2
ATOM  1879 N   LEU  276     37.124  38.114  28.506  1.00 52.23      B2
ATOM  1880 H   LEU  276     37.350  38.722  29.233  1.00  0.00      B2
ATOM  1881 CA  LEU  276     38.091  37.163  28.066  1.00 48.93      B2
ATOM  1882 CB  LEU  276     39.483  37.564  28.542  1.00 45.96      B2
ATOM  1883 CG  LEU  276     40.241  38.557  27.670  1.00 43.20      B2
ATOM  1884 CD1 LEU  276     41.599  38.782  28.279  1.00 44.63      B2
ATOM  1885 CD2 LEU  276     40.429  38.033  26.271  1.00 40.55      B2
ATOM  1886 C   LEU  276     37.673  35.833  28.638  1.00 47.84      B2
ATOM  1887 O   LEU  276     37.784  34.803  27.964  1.00 48.51      B2
ATOM  1888 N   ALA  277     37.074  35.840  29.804  1.00 45.56      B2
ATOM  1889 H   ALA  277     36.898  36.662  30.289  1.00  0.00      B2
ATOM  1890 CA  ALA  277     36.613  34.605  30.365  1.00 45.77      B2
ATOM  1891 CB  ALA  277     36.147  34.810  31.783  1.00 47.87      B2
ATOM  1892 C   ALA  277     35.442  34.111  29.542  1.00 45.03      B2
ATOM  1893 O   ALA  277     35.342  32.926  29.271  1.00 44.20      B2
ATOM  1894 N   GLN  278     34.592  35.000  29.049  1.00 45.13      B2
ATOM  1895 H   GLN  278     34.731  35.944  29.263  1.00  0.00      B2
ATOM  1896 CA  GLN  278     33.435  34.601  28.284  1.00 45.27      B2
ATOM  1897 CB  GLN  278     32.550  35.825  28.083  1.00 48.13      B2
ATOM  1898 CG  GLN  278     31.140  35.442  28.484  1.00 56.00      B2
ATOM  1899 CD  GLN  278     30.045  36.464  28.178  1.00 61.94      B2
ATOM  1900 OE1 GLN  278     29.048  36.530  28.896  1.00 65.95      B2
ATOM  1901 NE2 GLN  278     30.080  37.291  27.132  1.00 65.55      B2
ATOM  1902 HE21 GLN  278     30.829  37.221  26.510  1.00  0.00      B2
ATOM  1903 HE22 GLN  278     29.343  37.927  27.056  1.00  0.00      B2
ATOM  1904 C   GLN  278     33.812  33.971  26.950  1.00 43.16      B2
ATOM  1905 O   GLN  278     33.173  33.050  26.462  1.00 40.58      B2
ATOM  1906 N   LEU  279     34.869  34.476  26.331  1.00 43.32      B2
ATOM  1907 H   LEU  279     35.328  35.227  26.767  1.00  0.00      B2
ATOM  1908 CA  LEU  279     35.398  33.966  25.069  1.00 42.80      B2
ATOM  1909 CB  LEU  279     36.583  34.790  24.626  1.00 41.42      B2
ATOM  1910 CG  LEU  279     36.885  35.014  23.190  1.00 40.76      B2
ATOM  1911 CD1 LEU  279     38.239  35.647  23.130  1.00 41.76      B2
ATOM  1912 CD2 LEU  279     36.943  33.753  22.411  1.00 40.01      B2
ATOM  1913 C   LEU  279     35.876  32.554  25.341  1.00 42.92      B2
ATOM  1914 O   LEU  279     35.572  31.598  24.640  1.00 42.57      B2
ATOM  1915 N   HIS  280     36.654  32.463  26.403  1.00 43.93      B2
ATOM  1916 H   HIS  280     36.837  33.282  26.917  1.00  0.00      B2
ATOM  1917 CA  HIS  280     37.215  31.223  26.850  1.00 46.12      B2
ATOM  1918 CB  HIS  280     38.029  31.506  28.101  1.00 48.74      B2
ATOM  1919 CG  HIS  280     38.914  30.320  28.394  1.00 54.16      B2
ATOM  1920 CD2 HIS  280     40.041  30.069  27.650  1.00 56.02      B2
ATOM  1921 ND1 HIS  280     38.759  29.326  29.264  1.00 56.01      B2
ATOM  1922 HD1 HIS  280     38.012  29.203  29.890  1.00  0.00      B2
ATOM  1923 CE1 HIS  280     39.744  28.483  29.058  1.00 56.64      B2
ATOM  1924 NE2 HIS  280     40.507  28.937  28.088  1.00 56.64      B2
ATOM  1925 HE2 HIS  280     41.282  28.478  27.684  1.00  0.00      B2
ATOM  1926 C   HIS  280     36.161  30.134  27.117  1.00 45.65      B2
ATOM  1927 O   HIS  280     36.362  28.977  26.711  1.00 46.23      B2
ATOM  1928 N   SER  281     35.086  30.473  27.822  1.00 43.91      B2
ATOM  1929 H   SER  281     35.009  31.367  28.219  1.00  0.00      B2
ATOM  1930 CA  SER  281     34.008  29.574  28.105  1.00 43.53      B2
ATOM  1931 CB  SER  281     33.026  30.291  29.002  1.00 44.18      B2
ATOM  1932 OG  SER  281     33.761  30.812  30.113  1.00 47.79      B2
ATOM  1933 HG  SER  281     33.288  30.648  30.931  1.00  0.00      B2
ATOM  1934 C   SER  281     33.382  29.169  26.787  1.00 43.45      B2
ATOM  1935 O   SER  281     33.334  27.973  26.496  1.00 44.84      B2
ATOM  1936 N   GLY  282     32.977  30.120  25.940  1.00 42.34      B2
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FIGURE 5

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ATOM  1937  H   GLY  282      33.043  31.058  26.221  1.00  0.00      B2
ATOM  1938  CA  GLY  282      32.363  29.869  24.632  1.00 40.65      B2
ATOM  1939  C   GLY  282      33.175  28.937  23.755  1.00 39.06      B2
ATOM  1940  O   GLY  282      32.584  28.075  23.107  1.00 40.10      B2
ATOM  1941  N   LEU  283      34.514  29.066  23.776  1.00 37.39      B2
ATOM  1942  H   LEU  283      34.880  29.807  24.304  1.00  0.00      B2
ATOM  1943  CA  LEU  283      35.465  28.213  23.037  1.00 35.06      B2
ATOM  1944  CB  LEU  283      36.902  28.718  23.089  1.00 30.20      B2
ATOM  1945  CG  LEU  283      37.167  30.001  22.302  1.00 25.73      B2
ATOM  1946  CD1 LEU  283      38.539  30.461  22.664  1.00 24.38      B2
ATOM  1947  CD2 LEU  283      37.036  29.802  20.815  1.00 21.94      B2
ATOM  1948  C   LEU  283      35.470  26.851  23.651  1.00 34.81      B2
ATOM  1949  O   LEU  283      35.314  25.859  22.947  1.00 31.09      B2
ATOM  1950  N   PHE  284      35.533  26.842  24.973  1.00 37.62      B2
ATOM  1951  H   PHE  284      35.567  27.686  25.467  1.00  0.00      B2
ATOM  1952  CA  PHE  284      35.485  25.596  25.710  1.00 42.51      B2
ATOM  1953  CB  PHE  284      35.542  25.877  27.184  1.00 49.49      B2
ATOM  1954  CG  PHE  284      36.221  24.770  27.968  1.00 58.39      B2
ATOM  1955  CD1 PHE  284      37.265  25.108  28.816  1.00 63.05      B2
ATOM  1956  CD2 PHE  284      35.810  23.453  27.861  1.00 60.84      B2
ATOM  1957  CE1 PHE  284      37.900  24.124  29.563  1.00 65.86      B2
ATOM  1958  CE2 PHE  284      36.444  22.480  28.605  1.00 64.49      B2
ATOM  1959  CZ  PHE  284      37.486  22.810  29.455  1.00 66.32      B2
ATOM  1960  C   PHE  284      34.204  24.849  25.384  1.00 41.44      B2
ATOM  1961  O   PHE  284      34.257  23.630  25.306  1.00 41.42      B2
ATOM  1962  N   LEU  285      33.100  25.563  25.101  1.00 41.24      B2
ATOM  1963  H   LEU  285      33.192  26.534  25.174  1.00  0.00      B2
ATOM  1964  CA  LEU  285      31.781  25.025  24.730  1.00 38.92      B2
ATOM  1965  CB  LEU  285      30.727  26.139  24.807  1.00 39.05      B2
ATOM  1966  CG  LEU  285      29.292  25.740  24.481  1.00 41.16      B2
ATOM  1967  CD1 LEU  285      28.711  24.981  25.662  1.00 41.12      B2
ATOM  1968  CD2 LEU  285      28.472  26.971  24.139  1.00 39.60      B2
ATOM  1969  C   LEU  285      31.780  24.441  23.329  1.00 37.34      B2
ATOM  1970  O   LEU  285      31.245  23.351  23.095  1.00 36.97      B2
ATOM  1971  N   TYR  286      32.352  25.172  22.372  1.00 35.26      B2
ATOM  1972  H   TYR  286      32.705  26.062  22.593  1.00  0.00      B2
ATOM  1973  CA  TYR  286      32.455  24.660  21.033  1.00 35.04      B2
ATOM  1974  CB  TYR  286      32.891  25.790  20.122  1.00 34.44      B2
ATOM  1975  CG  TYR  286      31.690  26.684  19.808  1.00 34.75      B2
ATOM  1976  CD1 TYR  286      31.433  27.879  20.469  1.00 35.67      B2
ATOM  1977  CE1 TYR  286      30.313  28.620  20.158  1.00 36.90      B2
ATOM  1978  CD2 TYR  286      30.823  26.255  18.839  1.00 36.19      B2
ATOM  1979  CE2 TYR  286      29.707  26.990  18.521  1.00 37.55      B2
ATOM  1980  CZ  TYR  286      29.449  28.164  19.178  1.00 37.73      B2
ATOM  1981  OH  TYR  286      28.285  28.826  18.823  1.00 38.04      B2
ATOM  1982  HH  TYR  286      28.289  29.707  19.243  1.00  0.00      B2
ATOM  1983  C   TYR  286      33.393  23.464  20.926  1.00 34.80      B2
ATOM  1984  O   TYR  286      33.071  22.537  20.180  1.00 35.35      B2
ATOM  1985  N   ALA  287      34.527  23.339  21.636  1.00 34.66      B2
ATOM  1986  H   ALA  287      34.803  24.088  22.206  1.00  0.00      B2
ATOM  1987  CA  ALA  287      35.350  22.108  21.565  1.00 34.28      B2
ATOM  1988  CB  ALA  287      36.617  22.291  22.415  1.00 33.63      B2
ATOM  1989  C   ALA  287      34.528  20.906  22.073  1.00 33.32      B2
ATOM  1990  O   ALA  287      34.535  19.827  21.478  1.00 33.07      B2
ATOM  1991  N   GLY  288      33.723  21.118  23.111  1.00 33.19      B2
ATOM  1992  H   GLY  288      33.791  21.985  23.564  1.00  0.00      B2
ATOM  1993  CA  GLY  288      32.761  20.162  23.655  1.00 35.62      B2
ATOM  1994  C   GLY  288      31.744  19.606  22.636  1.00 36.89      B2
ATOM  1995  O   GLY  288      31.624  18.379  22.444  1.00 34.97      B2
ATOM  1996  N   LEU  289      31.037  20.536  21.966  1.00 36.69      B2
ATOM  1997  H   LEU  289      31.200  21.476  22.201  1.00  0.00      B2
ATOM  1998  CA  LEU  289      30.018  20.249  20.954  1.00 35.05      B2
ATOM  1999  CB  LEU  289      29.351  21.576  20.502  1.00 36.32      B2
ATOM  2000  CG  LEU  289      28.552  22.450  21.464  1.00 35.76      B2
ATOM  2001  CD1 LEU  289      28.256  23.821  20.890  1.00 32.66      B2
ATOM  2002  CD2 LEU  289      27.246  21.780  21.697  1.00 35.35      B2
ATOM  2003  C   LEU  289      30.536  19.519  19.714  1.00 34.21      B2
ATOM  2004  O   LEU  289      29.871  18.694  19.078  1.00 33.28      B2
ATOM  2005  N   LEU  290      31.756  19.902  19.355  1.00 33.25      B2
ATOM  2006  H   LEU  290      32.183  20.634  19.850  1.00  0.00      B2
ATOM  2007  CA  LEU  290      32.448  19.345  18.230  1.00 32.44      B2
ATOM  2008  CB  LEU  290      33.729  20.159  18.000  1.00 32.62      B2
ATOM  2009  CG  LEU  290      33.560  21.509  17.315  1.00 32.05      B2
ATOM  2010  CD1 LEU  290      34.889  22.189  17.349  1.00 32.58      B2
ATOM  2011  CD2 LEU  290      33.068  21.374  15.879  1.00 31.74      B2
ATOM  2012  C   LEU  290      32.737  17.908  18.558  1.00 31.94      B2
ATOM  2013  O   LEU  290      32.432  17.020  17.772  1.00 30.50      B2
ATOM  2014  N   GLN  291      33.249  17.711  19.770  1.00 33.58      B2
ATOM  2015  H   GLN  291      33.512  18.494  20.298  1.00  0.00      B2
ATOM  2016  CA  GLN  291      33.499  16.372  20.311  1.00 36.39      B2
ATOM  2017  CB  GLN  291      33.988  16.490  21.702  1.00 36.86      B2
ATOM  2018  CG  GLN  291      34.926  15.367  21.950  1.00 39.48      B2
ATOM  2019  CD  GLN  291      35.658  15.503  23.252  1.00 40.79      B2
ATOM  2020  OE1 GLN  291      36.457  14.626  23.549  1.00 44.80      B2
ATOM  2021  NE2 GLN  291      35.494  16.535  24.072  1.00 42.59      B2
ATOM  2022 HE21 GLN  291      34.928  17.287  23.817  1.00  0.00      B2
ATOM  2023 HE22 GLN  291      35.910  16.463  24.958  1.00  0.00      B2
ATOM  2024  C   GLN  291      32.233  15.536  20.307  1.00 36.66      B2
ATOM  2025  O   GLN  291      32.220  14.478  19.707  1.00 37.46      B2
ATOM  2026  N   ALA  292      31.143  16.023  20.913  1.00 38.37      B2
ATOM  2027  H   ALA  292      31.255  16.849  21.418  1.00  0.00      B2
ATOM  2028  CA  ALA  292      29.778  15.451  20.857  1.00 39.25      B2
ATOM  2029  CB  ALA  292      28.818  16.485  21.444  1.00 40.28      B2
ATOM  2030  C   ALA  292      29.215  14.999  19.484  1.00 38.65      B2
ATOM  2031  O   ALA  292      28.411  14.067  19.356  1.00 37.58      B2
ATOM  2032  N   LEU  293      29.614  15.702  18.430  1.00 39.00      B2
ATOM  2033  H   LEU  293      30.149  16.513  18.574  1.00  0.00      B2
ATOM  2034  CA  LEU  293      29.265  15.335  17.077  1.00 39.74      B2
ATOM  2035  CB  LEU  293      29.662  16.418  16.106  1.00 37.53      B2
ATOM  2036  CG  LEU  293      28.969  17.701  16.138  1.00 34.34      B2
ATOM  2037  CD1 LEU  293      29.547  18.582  15.053  1.00 33.88      B2
ATOM  2038  CD2 LEU  293      27.503  17.462  15.918  1.00 35.60      B2
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FIGURE 5

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ATOM  2039 C   LEU  293     29.933  14.060  16.596  1.00 40.86      B2
ATOM  2040 O   LEU  293     29.686  13.669  15.449  1.00 40.58      B2
ATOM  2041 N   GLU  294     30.887  13.495  17.365  1.00 42.12      B2
ATOM  2042 H   GLU  294     31.131  13.963  18.190  1.00  0.00      B2
ATOM  2043 CA  GLU  294     31.598  12.253  17.076  1.00 42.89      B2
ATOM  2044 CB  GLU  294     30.806  10.984  17.485  1.00 48.38      B2
ATOM  2045 CG  GLU  294     30.715  10.614  18.972  1.00 56.26      B2
ATOM  2046 CD  GLU  294     29.271  10.408  19.486  1.00 63.70      B2
ATOM  2047 OE1 GLU  294     29.058  10.603  20.702  1.00 67.72      B2
ATOM  2048 OE2 GLU  294     28.363  10.074  18.692  1.00 64.81      B2
ATOM  2049 C   GLU  294     31.972  12.068  15.632  1.00 41.53      B2
ATOM  2050 O   GLU  294     31.804  11.007  15.021  1.00 40.29      B2
ATOM  2051 N   GLY  295     32.424  13.203  15.106  1.00 40.93      B2
ATOM  2052 H   GLY  295     32.357  14.033  15.621  1.00  0.00      B2
ATOM  2053 CA  GLY  295     32.998  13.236  13.783  1.00 39.95      B2
ATOM  2054 C   GLY  295     32.027  13.230  12.634  1.00 40.60      B2
ATOM  2055 O   GLY  295     32.477  13.216  11.487  1.00 40.96      B2
ATOM  2056 N   ILE  296     30.728  13.296  12.898  1.00 41.18      B2
ATOM  2057 H   ILE  296     30.446  13.210  13.825  1.00  0.00      B2
ATOM  2058 CA  ILE  296     29.687  13.306  11.888  1.00 44.02      B2
ATOM  2059 CB  ILE  296     29.683  14.580  11.009  1.00 43.49      B2
ATOM  2060 CG2 ILE  296     28.288  14.685  10.421  1.00 40.56      B2
ATOM  2061 CG1 ILE  296     30.047  15.831  11.793  1.00 45.11      B2
ATOM  2062 CD  ILE  296     30.039  17.189  11.062  1.00 46.06      B2
ATOM  2063 C   ILE  296     29.820  12.107  10.949  1.00 46.71      B2
ATOM  2064 O   ILE  296     28.918  11.279  11.060  1.00 50.61      B2
ATOM  2065 N   SER  297     30.767  11.875  10.019  1.00 47.21      B2
ATOM  2066 H   SER  297     31.526  12.491  9.936  1.00  0.00      B2
ATOM  2067 CA  SER  297     30.810  10.646  9.234  1.00 46.73      B2
ATOM  2068 CB  SER  297     30.239  10.884  7.865  1.00 45.48      B2
ATOM  2069 OG  SER  297     30.988  11.782  7.072  1.00 46.27      B2
ATOM  2070 HG  SER  297     30.321  12.200  6.503  1.00  0.00      B2
ATOM  2071 C   SER  297     32.263  10.269  9.123  1.00 48.72      B2
ATOM  2072 O   SER  297     33.120  11.122  9.391  1.00 50.55      B2
ATOM  2073 N   PRO  298     32.655  9.069  8.697  1.00 49.68      B2
ATOM  2074 CD  PRO  298     31.782  7.964  8.334  1.00 50.62      B2
ATOM  2075 CA  PRO  298     34.049  8.701  8.458  1.00 50.33      B2
ATOM  2076 CB  PRO  298     33.948  7.308  7.856  1.00 51.53      B2
ATOM  2077 CG  PRO  298     32.576  7.266  7.231  1.00 50.43      B2
ATOM  2078 C   PRO  298     34.795  9.692  7.579  1.00 50.08      B2
ATOM  2079 O   PRO  298     35.883  10.137  7.930  1.00 50.50      B2
ATOM  2080 N   GLN  299     34.173  10.086  6.469  1.00 50.48      B2
ATOM  2081 H   GLN  299     33.279  9.729  6.296  1.00  0.00      B2
ATOM  2082 CA  GLN  299     34.749  11.050  5.550  1.00 51.74      B2
ATOM  2083 CB  GLN  299     33.898  11.236  4.301  1.00 54.33      B2
ATOM  2084 CG  GLN  299     33.095  10.067  3.725  1.00 58.11      B2
ATOM  2085 CD  GLN  299     31.658  10.086  4.259  1.00 61.49      B2
ATOM  2086 OE1 GLN  299     31.160  9.083  4.776  1.00 61.00      B2
ATOM  2087 NE2 GLN  299     30.942  11.217  4.204  1.00 62.12      B2
ATOM  2088 HE21 GLN  299     31.345  12.012  3.800  1.00  0.00      B2
ATOM  2089 HE22 GLN  299     30.034  11.191  4.566  1.00  0.00      B2
ATOM  2090 C   GLN  299     34.923  12.453  6.160  1.00 51.04      B2
ATOM  2091 O   GLN  299     35.796  13.186  5.718  1.00 53.38      B2
ATOM  2092 N   LEU  300     34.118  12.918  7.120  1.00 48.65      B2
ATOM  2093 H   LEU  300     33.382  12.351  7.437  1.00  0.00      B2
ATOM  2094 CA  LEU  300     34.272  14.220  7.745  1.00 43.92      B2
ATOM  2095 CB  LEU  300     32.856  14.719  8.021  1.00 41.39      B2
ATOM  2096 CG  LEU  300     32.073  15.546  6.974  1.00 37.99      B2
ATOM  2097 CD1 LEU  300     31.872  14.824  5.688  1.00 38.34      B2
ATOM  2098 CD2 LEU  300     30.705  15.809  7.527  1.00 37.67      B2
ATOM  2099 C   LEU  300     35.142  14.220  9.019  1.00 42.84      B2
ATOM  2100 O   LEU  300     35.558  15.278  9.541  1.00 41.56      B2
ATOM  2101 N   GLY  301     35.467  13.016  9.528  1.00 40.83      B2
ATOM  2102 H   GLY  301     35.157  12.221  9.046  1.00  0.00      B2
ATOM  2103 CA  GLY  301     36.199  12.826  10.779  1.00 36.72      B2
ATOM  2104 C   GLY  301     37.500  13.607  10.887  1.00 37.69      B2
ATOM  2105 O   GLY  301     37.665  14.406  11.809  1.00 37.31      B2
ATOM  2106 N   PRO  302     38.468  13.452  9.985  1.00 37.33      B2
ATOM  2107 CD  PRO  302     38.353  12.630  8.790  1.00 37.77      B2
ATOM  2108 CA  PRO  302     39.676  14.281  9.864  1.00 37.60      B2
ATOM  2109 CB  PRO  302     40.256  13.907  8.541  1.00 36.62      B2
ATOM  2110 CG  PRO  302     39.047  13.487  7.745  1.00 37.94      B2
ATOM  2111 C   PRO  302     39.486  15.782  10.033  1.00 37.45      B2
ATOM  2112 O   PRO  302     40.132  16.398  10.901  1.00 38.33      B2
ATOM  2113 N   THR  303     38.547  16.311  9.204  1.00 37.05      B2
ATOM  2114 H   THR  303     38.085  15.727  8.567  1.00  0.00      B2
ATOM  2115 CA  THR  303     38.119  17.705  9.128  1.00 35.81      B2
ATOM  2116 CB  THR  303     36.963  17.770  8.123  1.00 37.26      B2
ATOM  2117 OG1 THR  303     37.416  17.161  6.909  1.00 39.64      B2
ATOM  2118 HG1 THR  303     37.369  17.785  6.178  1.00  0.00      B2
ATOM  2119 CG2 THR  303     36.469  19.204  7.927  1.00 38.55      B2
ATOM  2120 C   THR  303     37.687  18.223  10.506  1.00 34.93      B2
ATOM  2121 O   THR  303     38.085  19.263  11.063  1.00 35.11      B2
ATOM  2122 N   LEU  304     36.928  17.366  11.159  1.00 33.76      B2
ATOM  2123 H   LEU  304     36.672  16.500  10.762  1.00  0.00      B2
ATOM  2124 CA  LEU  304     36.436  17.746  12.418  1.00 31.01      B2
ATOM  2125 CB  LEU  304     35.345  16.803  12.708  1.00 30.31      B2
ATOM  2126 CG  LEU  304     34.234  17.567  13.320  1.00 31.32      B2
ATOM  2127 CD1 LEU  304     33.121  17.626  12.309  1.00 28.87      B2
ATOM  2128 CD2 LEU  304     33.921  16.970  14.692  1.00 34.23      B2
ATOM  2129 C   LEU  304     37.553  17.726  13.421  1.00 31.86      B2
ATOM  2130 O   LEU  304     37.615  18.623  14.259  1.00 34.24      B2
ATOM  2131 N   ASP  305     38.510  16.811  13.326  1.00 30.56      B2
ATOM  2132 H   ASP  305     38.456  16.117  12.635  1.00  0.00      B2
ATOM  2133 CA  ASP  305     39.576  16.797  14.303  1.00 30.72      B2
ATOM  2134 CB  ASP  305     40.504  15.608  14.114  1.00 36.20      B2
ATOM  2135 CG  ASP  305     39.912  14.201  14.288  1.00 40.64      B2
ATOM  2136 OD1 ASP  305     38.976  14.040  15.103  1.00 37.52      B2
ATOM  2137 OD2 ASP  305     40.426  13.304  13.581  1.00 42.39      B2
ATOM  2138 C   ASP  305     40.435  18.034  14.238  1.00 27.56      B2
ATOM  2139 O   ASP  305     40.775  18.575  15.311  1.00 24.61      B2
ATOM  2140 N   THR  306     40.781  18.417  12.979  1.00 24.77      B2
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FIGURE 5

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ATOM 2141 H  THR 306   40.469 17.875 12.230 1.00 0.00   B2
ATOM 2142 CA THR 306   41.553 19.633 12.751 1.00 24.39  B2
ATOM 2143 CB THR 306   41.665 19.931 11.318 1.00 24.58  B2
ATOM 2144 OG1 THR 306  42.074 18.753 10.665 1.00 25.13  B2
ATOM 2145 HG1 THR 306  41.447 18.029 10.768 1.00 0.00   B2
ATOM 2146 CG2 THR 306  42.690 21.027 11.089 1.00 25.77  B2
ATOM 2147 C  THR 306   40.893 20.844 13.419 1.00 25.24  B2
ATOM 2148 O  THR 306   41.488 21.472 14.296 1.00 27.24  B2
ATOM 2149 N  LEU 307   39.615 21.134 13.139 1.00 25.91  B2
ATOM 2150 H  LEU 307   39.125 20.547 12.520 1.00 0.00   B2
ATOM 2151 CA LEU 307   38.900 22.228 13.764 1.00 25.53  B2
ATOM 2152 CB LEU 307   37.571 22.170 13.142 1.00 25.09  B2
ATOM 2153 CG LEU 307   36.530 23.097 13.588 1.00 27.93  B2
ATOM 2154 CD1 LEU 307  37.008 24.515 13.484 1.00 29.87  B2
ATOM 2155 CD2 LEU 307  35.311 22.846 12.728 1.00 28.93  B2
ATOM 2156 C  LEU 307   38.850 22.214 15.269 1.00 27.09  B2
ATOM 2157 O  LEU 307   38.854 23.253 15.925 1.00 30.03  B2
ATOM 2158 N  GLN 308   38.875 21.044 15.879 1.00 29.09  B2
ATOM 2159 H  GLN 308   38.883 20.239 15.319 1.00 0.00   B2
ATOM 2160 CA GLN 308   38.824 20.848 17.340 1.00 29.36  B2
ATOM 2161 CB GLN 308   38.379 19.399 17.562 1.00 29.41  B2
ATOM 2162 CG GLN 308   37.862 19.140 18.935 1.00 32.24  B2
ATOM 2163 CD GLN 308   37.586 17.672 19.165 1.00 34.03  B2
ATOM 2164 OE1 GLN 308  36.973 17.023 18.311 1.00 33.48  B2
ATOM 2165 NE2 GLN 308  38.053 17.127 20.299 1.00 31.67  B2
ATOM 2166 HE21 GLN 308 38.547 17.697 20.917 1.00 0.00   B2
ATOM 2167 HE22 GLN 308 37.875 16.174 20.436 1.00 0.00   B2
ATOM 2168 C  GLN 308   40.154 21.138 18.051 1.00 28.94  B2
ATOM 2169 O  GLN 308   40.196 21.796 19.101 1.00 28.44  B2
ATOM 2170 N  LEU 309   41.269 20.671 17.460 1.00 28.78  B2
ATOM 2171 H  LEU 309   41.157 20.120 16.655 1.00 0.00   B2
ATOM 2172 CA LEU 309   42.632 20.923 17.967 1.00 28.56  B2
ATOM 2173 CB LEU 309   43.671 20.154 17.106 1.00 26.54  B2
ATOM 2174 CG LEU 309   43.632 18.636 17.241 1.00 24.98  B2
ATOM 2175 CD1 LEU 309  44.595 17.935 16.353 1.00 24.17  B2
ATOM 2176 CD2 LEU 309  43.992 18.310 18.621 1.00 23.45  B2
ATOM 2177 C  LEU 309   42.893 22.416 17.909 1.00 28.24  B2
ATOM 2178 O  LEU 309   43.370 22.957 18.907 1.00 30.32  B2
ATOM 2179 N  ASP 310   42.548 23.027 16.749 1.00 26.58  B2
ATOM 2180 H  ASP 310   42.296 22.437 16.007 1.00 0.00   B2
ATOM 2181 CA ASP 310   42.495 24.477 16.495 1.00 27.90  B2
ATOM 2182 CB ASP 310   42.025 24.659 15.076 1.00 28.41  B2
ATOM 2183 CG ASP 310   43.162 24.556 14.096 1.00 31.84  B2
ATOM 2184 OD1 ASP 310  42.959 24.766 12.905 1.00 31.54  B2
ATOM 2185 OD2 ASP 310  44.297 24.314 14.514 1.00 37.32  B2
ATOM 2186 C  ASP 310   41.666 25.410 17.422 1.00 27.99  B2
ATOM 2187 O  ASP 310   42.219 26.429 17.876 1.00 27.23  B2
ATOM 2188 N  VAL 311   40.374 25.086 17.725 1.00 26.29  B2
ATOM 2189 H  VAL 311   39.961 24.347 17.225 1.00 0.00   B2
ATOM 2190 CA VAL 311   39.546 25.803 18.706 1.00 24.29  B2
ATOM 2191 CB VAL 311   38.098 25.217 18.869 1.00 21.47  B2
ATOM 2192 CG1 VAL 311  37.341 25.915 19.949 1.00 19.01  B2
ATOM 2193 CG2 VAL 311  37.261 25.488 17.667 1.00 18.56  B2
ATOM 2194 C  VAL 311   40.270 25.638 20.020 1.00 27.21  B2
ATOM 2195 O  VAL 311   40.437 26.647 20.719 1.00 29.71  B2
ATOM 2196 N  ALA 312   40.762 24.428 20.357 1.00 27.97  B2
ATOM 2197 H  ALA 312   40.585 23.674 19.756 1.00 0.00   B2
ATOM 2198 CA ALA 312   41.515 24.157 21.583 1.00 29.24  B2
ATOM 2199 CB ALA 312   41.855 22.688 21.532 1.00 30.53  B2
ATOM 2200 C  ALA 312   42.778 25.026 21.784 1.00 30.06  B2
ATOM 2201 O  ALA 312   43.057 25.508 22.886 1.00 30.04  B2
ATOM 2202 N  ASP 313   43.554 25.286 20.735 1.00 31.33  B2
ATOM 2203 H  ASP 313   43.433 24.730 19.935 1.00 0.00   B2
ATOM 2204 CA ASP 313   44.610 26.275 20.743 1.00 34.22  B2
ATOM 2205 CB ASP 313   45.279 26.512 19.447 1.00 38.87  B2
ATOM 2206 CG ASP 313   46.071 25.404 18.866 1.00 44.55  B2
ATOM 2207 OD1 ASP 313  46.225 25.439 17.636 1.00 48.67  B2
ATOM 2208 OD2 ASP 313  46.521 24.553 19.647 1.00 49.25  B2
ATOM 2209 C  ASP 313   44.187 27.699 21.059 1.00 35.12  B2
ATOM 2210 O  ASP 313   44.807 28.390 21.894 1.00 38.60  B2
ATOM 2211 N  PHE 314   43.192 28.216 20.349 1.00 33.36  B2
ATOM 2212 H  PHE 314   42.784 27.683 19.619 1.00 0.00   B2
ATOM 2213 CA PHE 314   42.715 29.548 20.600 1.00 31.09  B2
ATOM 2214 CB PHE 314   41.572 29.860 19.631 1.00 32.06  B2
ATOM 2215 CG PHE 314   41.074 31.303 19.636 1.00 33.37  B2
ATOM 2216 CD1 PHE 314  39.780 31.568 19.247 1.00 31.81  B2
ATOM 2217 CD2 PHE 314  41.907 32.354 20.021 1.00 35.65  B2
ATOM 2218 CE1 PHE 314  39.318 32.857 19.240 1.00 29.15  B2
ATOM 2219 CE2 PHE 314  41.455 33.648 20.017 1.00 32.48  B2
ATOM 2220 CZ PHE 314   40.154 33.870 19.622 1.00 32.81  B2
ATOM 2221 C  PHE 314   42.282 29.601 22.057 1.00 29.90  B2
ATOM 2222 O  PHE 314   42.658 30.550 22.764 1.00 26.87  B2
ATOM 2223 N  ALA 315   41.686 28.532 22.584 1.00 29.29  B2
ATOM 2224 H  ALA 315   41.448 27.764 22.022 1.00 0.00   B2
ATOM 2225 CA ALA 315   41.300 28.583 23.961 1.00 31.61  B2
ATOM 2226 CB ALA 315   40.632 27.358 24.451 1.00 32.23  B2
ATOM 2227 C  ALA 315   42.482 28.751 24.836 1.00 34.41  B2
ATOM 2228 O  ALA 315   42.361 29.437 25.853 1.00 37.66  B2
ATOM 2229 N  THR 316   43.646 28.250 24.476 1.00 36.16  B2
ATOM 2230 H  THR 316   43.745 27.778 23.625 1.00 0.00   B2
ATOM 2231 CA THR 316   44.780 28.388 25.374 1.00 37.99  B2
ATOM 2232 CB THR 316   45.795 27.255 25.156 1.00 41.16  B2
ATOM 2233 OG1 THR 316  45.049 26.081 25.521 1.00 45.50  B2
ATOM 2234 HG1 THR 316  44.316 25.900 24.913 1.00 0.00   B2
ATOM 2235 CG2 THR 316  47.152 27.415 25.888 1.00 40.31  B2
ATOM 2236 C  THR 316   45.458 29.710 25.177 1.00 38.47  B2
ATOM 2237 O  THR 316   45.903 30.189 26.217 1.00 39.64  B2
ATOM 2238 N  THR 317   45.620 30.287 23.970 1.00 36.58  B2
ATOM 2239 H  THR 317   45.351 29.800 23.164 1.00 0.00   B2
ATOM 2240 CA THR 317   46.092 31.657 23.844 1.00 37.07  B2
ATOM 2241 CB THR 317   45.866 32.098 22.392 1.00 36.01  B2
ATOM 2242 OG1 THR 317  46.752 31.352 21.575 1.00 35.11  B2
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FIGURE 5

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ATOM  2243 HG1 THR  317      46.489  30.441  21.389  1.00  0.00      B2
ATOM  2244 CG2 THR  317      46.109  33.566  22.156  1.00 34.30      B2
ATOM  2245  C  THR  317      45.338  32.597  24.832  1.00 39.30      B2
ATOM  2246  O  THR  317      45.941  33.378  25.583  1.00 40.17      B2
ATOM  2247  N  ILE  318      44.003  32.481  24.912  1.00 40.83      B2
ATOM  2248  H  ILE  318      43.554  31.819  24.342  1.00  0.00      B2
ATOM  2249  CA ILE  318      43.172  33.317  25.788  1.00 40.75      B2
ATOM  2250  CB ILE  318      41.621  32.979  25.567  1.00 37.17      B2
ATOM  2251 CG2 ILE  318      40.742  33.706  26.545  1.00 34.29      B2
ATOM  2252 CG1 ILE  318      41.216  33.310  24.160  1.00 31.39      B2
ATOM  2253 CD  ILE  318      41.626  34.657  23.614  1.00 29.66      B2
ATOM  2254  C  ILE  318      43.624  33.019  27.217  1.00 42.43      B2
ATOM  2255  O  ILE  318      44.064  33.963  27.856  1.00 42.54      B2
ATOM  2256  N  TRP  319      43.662  31.784  27.744  1.00 44.17      B2
ATOM  2257  H  TRP  319      43.537  31.008  27.163  1.00  0.00      B2
ATOM  2258  CA TRP  319      43.994  31.633  29.142  1.00 46.90      B2
ATOM  2259  CB TRP  319      43.892  30.179  29.597  1.00 50.64      B2
ATOM  2260  CG TRP  319      43.998  30.094  31.131  1.00 56.05      B2
ATOM  2261 CD2 TRP  319      43.005  30.397  32.038  1.00 58.61      B2
ATOM  2262 CE2 TRP  319      43.685  30.281  33.251  1.00 60.50      B2
ATOM  2263 CE3 TRP  319      41.668  30.740  32.005  1.00 60.12      B2
ATOM  2264 CD1 TRP  319      45.188  29.788  31.760  1.00 58.07      B2
ATOM  2265 NE1 TRP  319      44.968  29.921  33.042  1.00 60.07      B2
ATOM  2266 HE1 TRP  319      45.637  29.765  33.740  1.00  0.00      B2
ATOM  2267 CZ2 TRP  319      43.044  30.512  34.456  1.00 61.00      B2
ATOM  2268 CZ3 TRP  319      41.022  30.967  33.210  1.00 61.58      B2
ATOM  2269 CH2 TRP  319      41.704  30.854  34.417  1.00 62.04      B2
ATOM  2270  C  TRP  319      45.398  32.136  29.456  1.00 47.85      B2
ATOM  2271  O  TRP  319      45.635  32.772  30.490  1.00 47.99      B2
ATOM  2272  N  GLN  320      46.339  31.915  28.550  1.00 48.63      B2
ATOM  2273  H  GLN  320      46.091  31.482  27.708  1.00  0.00      B2
ATOM  2274  CA GLN  320      47.706  32.319  28.767  1.00 49.45      B2
ATOM  2275  CB GLN  320      48.567  31.988  27.589  1.00 51.44      B2
ATOM  2276  CG GLN  320      48.828  30.494  27.444  1.00 55.03      B2
ATOM  2277  CD GLN  320      49.958  30.349  26.438  1.00 60.17      B2
ATOM  2278 OE1 GLN  320      51.116  30.465  26.834  1.00 65.26      B2
ATOM  2279 NE2 GLN  320      49.771  30.145  25.131  1.00 59.32      B2
ATOM  2280 HE21 GLN  320      48.859  30.087  24.789  1.00  0.00      B2
ATOM  2281 HE22 GLN  320      50.582  30.083  24.590  1.00  0.00      B2
ATOM  2282  C  GLN  320      47.717  33.790  28.983  1.00 49.62      B2
ATOM  2283  O  GLN  320      48.251  34.209  29.987  1.00 49.91      B2
ATOM  2284  N  GLN  321      46.998  34.538  28.150  1.00 51.76      B2
ATOM  2285  H  GLN  321      46.535  34.102  27.403  1.00  0.00      B2
ATOM  2286  CA GLN  321      46.837  35.988  28.278  1.00 52.08      B2
ATOM  2287  CB GLN  321      46.015  36.571  27.151  1.00 49.72      B2
ATOM  2288  CG GLN  321      45.873  38.058  27.166  1.00 51.19      B2
ATOM  2289  CD GLN  321      47.211  38.781  27.201  1.00 53.13      B2
ATOM  2290 OE1 GLN  321      48.090  38.622  26.364  1.00 55.36      B2
ATOM  2291 NE2 GLN  321      47.468  39.618  28.177  1.00 53.21      B2
ATOM  2292 HE21 GLN  321      46.800  39.713  28.889  1.00  0.00      B2
ATOM  2293 HE22 GLN  321      48.338  40.057  28.168  1.00  0.00      B2
ATOM  2294  C  GLN  321      46.112  36.315  29.562  1.00 54.30      B2
ATOM  2295  O  GLN  321      46.293  37.422  30.058  1.00 54.39      B2
ATOM  2296  N  MET  322      45.269  35.441  30.117  1.00 54.50      B2
ATOM  2297  H  MET  322      45.098  34.592  29.662  1.00  0.00      B2
ATOM  2298  CA MET  322      44.619  35.748  31.375  1.00 55.42      B2
ATOM  2299  CB MET  322      43.595  34.690  31.713  1.00 52.94      B2
ATOM  2300  CG MET  322      42.527  34.865  30.658  1.00 51.76      B2
ATOM  2301  SD MET  322      40.861  34.428  31.189  1.00 54.19      B2
ATOM  2302  CE MET  322      40.293  33.192  30.069  1.00 52.53      B2
ATOM  2303  C  MET  322      45.700  35.811  32.432  1.00 57.69      B2
ATOM  2304  O  MET  322      45.781  36.739  33.248  1.00 57.85      B2
ATOM  2305  N  GLU  323      46.652  34.900  32.319  1.00 60.28      B2
ATOM  2306  H  GLU  323      46.637  34.296  31.544  1.00  0.00      B2
ATOM  2307  CA GLU  323      47.741  34.875  33.273  1.00 62.99      B2
ATOM  2308  CB GLU  323      48.558  33.635  32.957  1.00 65.81      B2
ATOM  2309  CG GLU  323      47.640  32.423  32.918  1.00 68.36      B2
ATOM  2310  CD GLU  323      48.303  31.125  33.310  1.00 71.21      B2
ATOM  2311 OE1 GLU  323      47.651  30.364  34.044  1.00 71.19      B2
ATOM  2312 OE2 GLU  323      49.451  30.900  32.884  1.00 72.43      B2
ATOM  2313  C  GLU  323      48.648  36.124  33.418  1.00 63.96      B2
ATOM  2314 OT1 GLU  323      48.782  36.492  34.584  1.00 64.11      B2
ATOM  2315 OT2 GLU  323      49.169  36.725  32.449  1.00 62.96      B2
ATOM  2316  CB MET  338      27.559  17.690  25.056  1.00 62.56      B3
ATOM  2317  CG MET  338      28.087  18.862  24.222  1.00 63.85      B3
ATOM  2318  SD MET  338      28.738  20.224  25.219  1.00 66.95      B3
ATOM  2319  CE MET  338      27.328  21.252  25.515  1.00 65.50      B3
ATOM  2320  C  MET  338      24.988  17.301  25.122  1.00 57.55      B3
ATOM  2321  O  MET  338      24.417  16.347  25.667  1.00 56.47      B3
ATOM  2322 HT1 MET  338      26.255  16.010  26.594  1.00  0.00      B3
ATOM  2323 HT2 MET  338      25.375  17.061  27.500  1.00  0.00      B3
ATOM  2324  N  MET  338      26.286  16.971  27.009  1.00 61.55      B3
ATOM  2325 HT3 MET  338      27.108  17.107  27.620  1.00  0.00      B3
ATOM  2326  CA MET  338      26.226  17.853  25.851  1.00 60.35      B3
ATOM  2327  N  PRO  339      24.493  17.830  23.998  1.00 55.58      B3
ATOM  2328  CD PRO  339      24.914  19.075  23.375  1.00 54.49      B3
ATOM  2329  CA PRO  339      23.453  17.226  23.164  1.00 54.62      B3
ATOM  2330  CB PRO  339      23.463  18.098  21.903  1.00 53.52      B3
ATOM  2331  CG PRO  339      24.845  18.711  21.909  1.00 53.04      B3
ATOM  2332  C  PRO  339      23.666  15.748  22.881  1.00 53.61      B3
ATOM  2333  O  PRO  339      24.730  15.222  23.169  1.00 53.35      B3
ATOM  2334  N  ALA  340      22.704  15.045  22.333  1.00 54.32      B3
ATOM  2335  H  ALA  340      21.844  15.460  22.111  1.00  0.00      B3
ATOM  2336  CA ALA  340      22.909  13.651  21.968  1.00 56.04      B3
ATOM  2337  CB ALA  340      21.867  12.713  22.625  1.00 57.60      B3
ATOM  2338  C  ALA  340      22.617  13.713  20.495  1.00 55.61      B3
ATOM  2339  O  ALA  340      21.426  13.783  20.196  1.00 58.64      B3
ATOM  2340  N  PHE  341      23.516  13.734  19.514  1.00 53.34      B3
ATOM  2341  H  PHE  341      24.472  13.607  19.685  1.00  0.00      B3
ATOM  2342  CA PHE  341      23.016  13.900  18.158  1.00 49.92      B3
ATOM  2343  CB PHE  341      24.050  14.541  17.244  1.00 48.16      B3
ATOM  2344  CG PHE  341      24.382  15.940  17.658  1.00 45.00      B3
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FIGURE 5

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ATOM 2345 CD1 PHE 341 23.510 16.923 17.359 1.00 43.44 B3
ATOM 2346 CD2 PHE 341 25.527 16.175 18.388 1.00 47.03 B3
ATOM 2347 CE1 PHE 341 23.812 18.172 17.831 1.00 49.15 B3
ATOM 2348 CE2 PHE 341 25.827 17.426 18.862 1.00 47.86 B3
ATOM 2349 CZ PHE 341 24.952 18.437 18.580 1.00 48.36 B3
ATOM 2350 C PHE 341 22.684 12.510 17.672 1.00 49.56 B3
ATOM 2351 O PHE 341 23.309 11.938 16.781 1.00 51.46 B3
ATOM 2352 N ALA 342 21.625 11.985 18.245 1.00 47.40 B3
ATOM 2353 H ALA 342 21.026 12.585 18.741 1.00 0.00 B3
ATOM 2354 CA ALA 342 21.167 10.650 17.997 1.00 46.11 B3
ATOM 2355 CB ALA 342 19.874 10.531 18.804 1.00 47.10 B3
ATOM 2356 C ALA 342 20.962 10.149 16.556 1.00 44.37 B3
ATOM 2357 O ALA 342 20.138 9.247 16.418 1.00 45.65 B3
ATOM 2358 N SER 343 21.537 10.573 15.423 1.00 41.37 B3
ATOM 2359 H SER 343 22.191 11.301 15.428 1.00 0.00 B3
ATOM 2360 CA SER 343 21.274 9.923 14.145 1.00 38.80 B3
ATOM 2361 CB SER 343 19.842 10.138 13.656 1.00 38.79 B3
ATOM 2362 OG SER 343 19.205 11.300 14.182 1.00 37.75 B3
ATOM 2363 HG SER 343 18.963 11.059 15.092 1.00 0.00 B3
ATOM 2364 C SER 343 22.172 10.467 13.088 1.00 38.22 B3
ATOM 2365 O SER 343 22.810 11.471 13.382 1.00 38.30 B3
ATOM 2366 N ALA 344 22.206 9.845 11.888 1.00 36.73 B3
ATOM 2367 H ALA 344 21.762 8.978 11.805 1.00 0.00 B3
ATOM 2368 CA ALA 344 22.914 10.384 10.715 1.00 38.09 B3
ATOM 2369 CB ALA 344 22.583 9.640 9.422 1.00 36.78 B3
ATOM 2370 C ALA 344 22.472 11.842 10.496 1.00 37.72 B3
ATOM 2371 O ALA 344 23.271 12.765 10.676 1.00 38.42 B3
ATOM 2372 N PHE 345 21.194 12.042 10.163 1.00 36.10 B3
ATOM 2373 H PHE 345 20.668 11.298 9.811 1.00 0.00 B3
ATOM 2374 CA PHE 345 20.564 13.338 10.195 1.00 34.69 B3
ATOM 2375 CB PHE 345 19.040 13.254 10.128 1.00 33.24 B3
ATOM 2376 CG PHE 345 18.462 14.656 9.918 1.00 31.72 B3
ATOM 2377 CD1 PHE 345 17.715 15.223 10.905 1.00 26.64 B3
ATOM 2378 CD2 PHE 345 18.767 15.343 8.745 1.00 29.99 B3
ATOM 2379 CE1 PHE 345 17.284 16.503 10.682 1.00 33.56 B3
ATOM 2380 CE2 PHE 345 18.333 16.619 8.537 1.00 30.81 B3
ATOM 2381 CZ PHE 345 17.581 17.201 9.520 1.00 31.44 B3
ATOM 2382 C PHE 345 20.888 14.145 11.458 1.00 35.02 B3
ATOM 2383 O PHE 345 21.246 15.319 11.292 1.00 37.81 B3
ATOM 2384 N GLN 346 20.814 13.688 12.691 1.00 32.53 B3
ATOM 2385 H GLN 346 20.516 12.778 12.894 1.00 0.00 B3
ATOM 2386 CA GLN 346 21.156 14.586 13.758 1.00 33.46 B3
ATOM 2387 CB GLN 346 20.899 13.985 15.061 1.00 33.80 B3
ATOM 2388 CG GLN 346 19.459 14.284 15.174 1.00 35.68 B3
ATOM 2389 CD GLN 346 18.788 13.658 16.344 1.00 38.48 B3
ATOM 2390 OE1 GLN 346 19.358 13.328 17.374 1.00 41.78 B3
ATOM 2391 NE2 GLN 346 17.508 13.463 16.167 1.00 41.08 B3
ATOM 2392 HE21 GLN 346 17.088 13.724 15.323 1.00 0.00 B3
ATOM 2393 HE22 GLN 346 17.026 13.063 16.919 1.00 0.00 B3
ATOM 2394 C GLN 346 22.564 15.051 13.773 1.00 35.73 B3
ATOM 2395 O GLN 346 22.766 16.231 14.051 1.00 38.18 B3
ATOM 2396 N ARG 347 23.507 14.190 13.431 1.00 35.57 B3
ATOM 2397 H ARG 347 23.248 13.289 13.157 1.00 0.00 B3
ATOM 2398 CA ARG 347 24.907 14.538 13.396 1.00 35.95 B3
ATOM 2399 CB ARG 347 25.760 13.236 13.222 1.00 36.29 B3
ATOM 2400 CG ARG 347 26.198 12.549 14.540 1.00 37.41 B3
ATOM 2401 CD ARG 347 26.986 11.246 14.373 1.00 39.70 B3
ATOM 2402 NE ARG 347 26.072 10.167 14.028 1.00 47.18 B3
ATOM 2403 HE ARG 347 25.416 9.893 14.701 1.00 0.00 B3
ATOM 2404 CZ ARG 347 26.071 9.516 12.846 1.00 48.49 B3
ATOM 2405 NH1 ARG 347 26.938 9.802 11.882 1.00 50.22 B3
ATOM 2406 HH11 ARG 347 27.602 10.528 12.031 1.00 0.00 B3
ATOM 2407 HH12 ARG 347 26.905 9.313 11.011 1.00 0.00 B3
ATOM 2408 NH2 ARG 347 25.130 8.608 12.574 1.00 48.46 B3
ATOM 2409 HH21 ARG 347 24.423 8.408 13.252 1.00 0.00 B3
ATOM 2410 HH22 ARG 347 25.126 8.131 11.697 1.00 0.00 B3
ATOM 2411 C ARG 347 25.183 15.544 12.267 1.00 35.54 B3
ATOM 2412 O ARG 347 25.877 16.549 12.445 1.00 36.73 B3
ATOM 2413 N ARG 348 24.611 15.353 11.096 1.00 34.74 B3
ATOM 2414 H ARG 348 24.043 14.559 11.005 1.00 0.00 B3
ATOM 2415 CA ARG 348 24.802 16.225 9.954 1.00 35.24 B3
ATOM 2416 CB ARG 348 24.091 15.623 8.751 1.00 36.76 B3
ATOM 2417 CG ARG 348 24.778 14.303 8.450 1.00 44.22 B3
ATOM 2418 CD ARG 348 24.014 13.379 7.529 1.00 49.23 B3
ATOM 2419 NE ARG 348 24.705 12.090 7.457 1.00 54.27 B3
ATOM 2420 HE ARG 348 25.300 11.836 8.193 1.00 0.00 B3
ATOM 2421 CZ ARG 348 24.557 11.226 6.430 1.00 53.75 B3
ATOM 2422 NH1 ARG 348 23.758 11.479 5.381 1.00 51.85 B3
ATOM 2423 HH11 ARG 348 23.234 12.329 5.339 1.00 0.00 B3
ATOM 2424 HH12 ARG 348 23.680 10.807 4.645 1.00 0.00 B3
ATOM 2425 NH2 ARG 348 25.252 10.083 6.462 1.00 54.51 B3
ATOM 2426 HH21 ARG 348 25.169 9.424 5.714 1.00 0.00 B3
ATOM 2427 HH22 ARG 348 25.860 9.894 7.232 1.00 0.00 B3
ATOM 2428 C ARG 348 24.283 17.629 10.237 1.00 34.80 B3
ATOM 2429 O ARG 348 25.078 18.564 10.219 1.00 35.16 B3
ATOM 2430 N ALA 349 23.008 17.795 10.607 1.00 33.85 B3
ATOM 2431 H ALA 349 22.470 16.984 10.755 1.00 0.00 B3
ATOM 2432 CA ALA 349 22.352 19.083 10.853 1.00 32.96 B3
ATOM 2433 CB ALA 349 20.809 18.894 11.070 1.00 33.36 B3
ATOM 2434 C ALA 349 22.945 19.746 12.083 1.00 31.84 B3
ATOM 2435 O ALA 349 22.981 20.969 12.210 1.00 30.69 B3
ATOM 2436 N GLY 350 23.444 18.954 13.018 1.00 31.30 B3
ATOM 2437 H GLY 350 23.308 17.984 12.976 1.00 0.00 B3
ATOM 2438 CA GLY 350 24.117 19.505 14.181 1.00 31.08 B3
ATOM 2439 C GLY 350 25.462 20.025 13.753 1.00 30.79 B3
ATOM 2440 O GLY 350 25.974 21.010 14.280 1.00 31.58 B3
ATOM 2441 N GLY 351 25.991 19.374 12.731 1.00 30.09 B3
ATOM 2442 H GLY 351 25.546 18.582 12.367 1.00 0.00 B3
ATOM 2443 CA GLY 351 27.263 19.735 12.184 1.00 29.95 B3
ATOM 2444 C GLY 351 27.182 21.097 11.534 1.00 29.25 B3
ATOM 2445 O GLY 351 27.937 21.974 11.919 1.00 28.73 B3
ATOM 2446 N VAL 352 26.336 21.285 10.522 1.00 28.92 B3
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FIGURE 5

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ATOM  2447  H   VAL  352      25.859  20.484  10.214  1.00  0.00      B3
ATOM  2448  CA  VAL  352      26.079  22.567   9.881  1.00 28.59      B3
ATOM  2449  CB  VAL  352      24.845  22.452   9.004  1.00 28.96      B3
ATOM  2450  CG1 VAL  352      24.627  23.785   8.346  1.00 30.86      B3
ATOM  2451  CG2 VAL  352      25.021  21.475   7.875  1.00 26.94      B3
ATOM  2452  C   VAL  352      25.849  23.709  10.890  1.00 29.29      B3
ATOM  2453  O   VAL  352      26.520  24.747  10.853  1.00 31.02      B3
ATOM  2454  N   LEU  353      24.923  23.543  11.819  1.00 27.52      B3
ATOM  2455  H   LEU  353      24.404  22.709  11.838  1.00  0.00      B3
ATOM  2456  CA  LEU  353      24.635  24.548  12.817  1.00 26.18      B3
ATOM  2457  CB  LEU  353      23.434  24.113  13.636  1.00 27.87      B3
ATOM  2458  CG  LEU  353      22.098  24.034  12.931  1.00 26.54      B3
ATOM  2459  CD1 LEU  353      21.064  23.617  13.924  1.00 25.49      B3
ATOM  2460  CD2 LEU  353      21.750  25.372  12.320  1.00 28.23      B3
ATOM  2461  C   LEU  353      25.742  24.905  13.772  1.00 27.17      B3
ATOM  2462  O   LEU  353      25.838  26.093  14.088  1.00 28.00      B3
ATOM  2463  N   VAL  354      26.539  23.949  14.318  1.00 27.20      B3
ATOM  2464  H   VAL  354      26.321  23.006  14.139  1.00  0.00      B3
ATOM  2465  CA  VAL  354      27.712  24.212  15.157  1.00 24.62      B3
ATOM  2466  CB  VAL  354      28.236  22.910  15.745  1.00 22.01      B3
ATOM  2467  CG1 VAL  354      29.568  23.089  16.406  1.00 19.82      B3
ATOM  2468  CG2 VAL  354      27.276  22.467  16.802  1.00 23.96      B3
ATOM  2469  C   VAL  354      28.812  24.893  14.332  1.00 25.46      B3
ATOM  2470  O   VAL  354      29.439  25.832  14.798  1.00 26.23      B3
ATOM  2471  N   ALA  355      29.059  24.530  13.089  1.00 26.12      B3
ATOM  2472  H   ALA  355      28.579  23.745  12.744  1.00  0.00      B3
ATOM  2473  CA  ALA  355      30.025  25.180  12.235  1.00 26.54      B3
ATOM  2474  CB  ALA  355      30.034  24.591  10.869  1.00 22.08      B3
ATOM  2475  C   ALA  355      29.533  26.601  12.096  1.00 28.51      B3
ATOM  2476  O   ALA  355      30.315  27.498  12.344  1.00 31.93      B3
ATOM  2477  N   SER  356      28.271  26.884  11.802  1.00 30.30      B3
ATOM  2478  H   SER  356      27.654  26.134  11.665  1.00  0.00      B3
ATOM  2479  CA  SER  356      27.778  28.249  11.625  1.00 31.10      B3
ATOM  2480  CB  SER  356      26.401  28.147  11.016  1.00 35.23      B3
ATOM  2481  OG  SER  356      25.679  29.380  10.905  1.00 43.82      B3
ATOM  2482  HG  SER  356      26.250  30.004  10.429  1.00  0.00      B3
ATOM  2483  C   SER  356      27.763  29.098  12.901  1.00 29.75      B3
ATOM  2484  O   SER  356      28.115  30.289  12.898  1.00 28.35      B3
ATOM  2485  N   HIS  357      27.465  28.464  14.025  1.00 27.82      B3
ATOM  2486  H   HIS  357      27.301  27.498  14.019  1.00  0.00      B3
ATOM  2487  CA  HIS  357      27.434  29.194  15.259  1.00 26.58      B3
ATOM  2488  CB  HIS  357      26.735  28.365  16.305  1.00 25.77      B3
ATOM  2489  CG  HIS  357      25.219  28.360  16.063  1.00 27.67      B3
ATOM  2490  CD2 HIS  357      24.563  28.767  14.915  1.00 28.94      B3
ATOM  2491  ND1 HIS  357      24.277  27.963  16.915  1.00 28.43      B3
ATOM  2492  HD1 HIS  357      24.456  27.622  17.828  1.00  0.00      B3
ATOM  2493  CE1 HIS  357      23.112  28.103  16.337  1.00 28.64      B3
ATOM  2494  NE2 HIS  357      23.298  28.589  15.130  1.00 29.48      B3
ATOM  2495  HE2 HIS  357      22.576  28.801  14.495  1.00  0.00      B3
ATOM  2496  C   HIS  357      28.852  29.506  15.645  1.00 27.93      B3
ATOM  2497  O   HIS  357      29.119  30.606  16.115  1.00 29.15      B3
ATOM  2498  N   LEU  358      29.830  28.637  15.383  1.00 28.33      B3
ATOM  2499  H   LEU  358      29.624  27.761  14.997  1.00  0.00      B3
ATOM  2500  CA  LEU  358      31.211  28.940  15.721  1.00 26.39      B3
ATOM  2501  CB  LEU  358      32.030  27.702  15.547  1.00 21.42      B3
ATOM  2502  CG  LEU  358      33.457  27.878  15.734  1.00 20.42      B3
ATOM  2503  CD1 LEU  358      33.805  28.078  17.165  1.00 16.79      B3
ATOM  2504  CD2 LEU  358      34.075  26.714  15.072  1.00 22.89      B3
ATOM  2505  C   LEU  358      31.721  30.067  14.822  1.00 26.45      B3
ATOM  2506  O   LEU  358      32.372  30.939  15.378  1.00 27.12      B3
ATOM  2507  N   GLN  359      31.460  30.130  13.518  1.00 26.41      B3
ATOM  2508  H   GLN  359      31.048  29.337  13.114  1.00  0.00      B3
ATOM  2509  CA  GLN  359      31.863  31.254  12.671  1.00 29.10      B3
ATOM  2510  CB  GLN  359      31.204  31.209  11.292  1.00 30.49      B3
ATOM  2511  CG  GLN  359      31.395  29.952  10.455  1.00 38.94      B3
ATOM  2512  CD  GLN  359      32.842  29.636  10.091  1.00 42.09      B3
ATOM  2513  OE1 GLN  359      33.774  29.979  10.821  1.00 46.15      B3
ATOM  2514  NE2 GLN  359      33.103  28.987   8.967  1.00 41.34      B3
ATOM  2515  HE21 GLN  359      32.341  28.706   8.412  1.00  0.00      B3
ATOM  2516  HE22 GLN  359      34.039  28.838   8.740  1.00  0.00      B3
ATOM  2517  C   GLN  359      31.512  32.621  13.254  1.00 29.39      B3
ATOM  2518  O   GLN  359      32.427  33.427  13.484  1.00 30.06      B3
ATOM  2519  N   SER  360      30.201  32.810  13.528  1.00 28.66      B3
ATOM  2520  H   SER  360      29.595  32.061  13.343  1.00  0.00      B3
ATOM  2521  CA  SER  360      29.570  34.003  14.071  1.00 27.35      B3
ATOM  2522  CB  SER  360      28.121  33.761  14.336  1.00 26.70      B3
ATOM  2523  OG  SER  360      27.493  33.539  13.078  1.00 29.72      B3
ATOM  2524  HG  SER  360      26.637  33.112  13.288  1.00  0.00      B3
ATOM  2525  C   SER  360      30.202  34.387  15.353  1.00 27.15      B3
ATOM  2526  O   SER  360      30.575  35.550  15.498  1.00 26.93      B3
ATOM  2527  N   PHE  361      30.383  33.403  16.246  1.00 25.38      B3
ATOM  2528  H   PHE  361      30.055  32.499  16.040  1.00  0.00      B3
ATOM  2529  CA  PHE  361      31.066  33.626  17.517  1.00 25.20      B3
ATOM  2530  CB  PHE  361      31.092  32.335  18.302  1.00 23.30      B3
ATOM  2531  CG  PHE  361      31.796  32.394  19.655  1.00 23.63      B3
ATOM  2532  CD1 PHE  361      31.127  32.854  20.777  1.00 22.44      B3
ATOM  2533  CD2 PHE  361      33.098  31.931  19.770  1.00 23.35      B3
ATOM  2534  CE1 PHE  361      31.772  32.834  22.000  1.00 22.78      B3
ATOM  2535  CE2 PHE  361      33.719  31.921  21.002  1.00 21.26      B3
ATOM  2536  CZ  PHE  361      33.058  32.368  22.114  1.00 19.54      B3
ATOM  2537  C   PHE  361      32.505  34.143  17.385  1.00 26.56      B3
ATOM  2538  O   PHE  361      32.914  34.979  18.183  1.00 26.76      B3
ATOM  2539  N   LEU  362      33.309  33.645  16.441  1.00 28.17      B3
ATOM  2540  H   LEU  362      32.962  32.921  15.874  1.00  0.00      B3
ATOM  2541  CA  LEU  362      34.679  34.089  16.222  1.00 28.89      B3
ATOM  2542  CB  LEU  362      35.452  33.125  15.338  1.00 28.18      B3
ATOM  2543  CG  LEU  362      35.603  31.656  15.781  1.00 29.61      B3
ATOM  2544  CD1 LEU  362      36.306  30.996  14.633  1.00 31.63      B3
ATOM  2545  CD2 LEU  362      36.374  31.433  17.055  1.00 26.38      B3
ATOM  2546  C   LEU  362      34.692  35.449  15.536  1.00 29.18      B3
ATOM  2547  O   LEU  362      35.649  36.202  15.748  1.00 27.43      B3
ATOM  2548  N   GLU  363      33.664  35.763  14.710  1.00 29.54      B3
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FIGURE 5

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ATOM  2549  H   GLU   363      33.009  35.066  14.495  1.00  0.00      B3
ATOM  2550  CA  GLU   363      33.496  37.090  14.145  1.00 30.30      B3
ATOM  2551  CB  GLU   363      32.357  37.147  13.228  1.00 30.90      B3
ATOM  2552  CG  GLU   363      32.763  36.735  11.849  1.00 38.69      B3
ATOM  2553  CD  GLU   363      33.642  37.662  11.013  1.00 42.62      B3
ATOM  2554  OE1 GLU   363      33.896  37.282   9.860  1.00 46.58      B3
ATOM  2555  OE2 GLU   363      34.051  38.734  11.488  1.00 46.47      B3
ATOM  2556  C   GLU   363      33.229  38.098  15.244  1.00 30.19      B3
ATOM  2557  O   GLU   363      33.837  39.167  15.239  1.00 30.26      B3
ATOM  2558  N   VAL   364      32.397  37.726  16.217  1.00 30.04      B3
ATOM  2559  H   VAL   364      31.888  36.898  16.100  1.00  0.00      B3
ATOM  2560  CA  VAL   364      32.178  38.522  17.400  1.00 31.90      B3
ATOM  2561  CB  VAL   364      31.014  38.021  18.269  1.00 31.41      B3
ATOM  2562  CG1 VAL   364      30.860  38.811  19.562  1.00 30.73      B3
ATOM  2563  CG2 VAL   364      29.750  38.200  17.497  1.00 29.96      B3
ATOM  2564  C   VAL   364      33.402  38.493  18.275  1.00 35.89      B3
ATOM  2565  O   VAL   364      33.683  39.535  18.855  1.00 37.54      B3
ATOM  2566  N   SER   365      34.173  37.421  18.477  1.00 38.25      B3
ATOM  2567  H   SER   365      33.971  36.577  18.030  1.00  0.00      B3
ATOM  2568  CA  SER   365      35.337  37.478  19.375  1.00 39.61      B3
ATOM  2569  CB  SER   365      36.041  36.113  19.555  1.00 43.00      B3
ATOM  2570  OG  SER   365      35.201  34.953  19.575  1.00 46.29      B3
ATOM  2571  HG  SER   365      34.270  35.189  19.644  1.00  0.00      B3
ATOM  2572  C   SER   365      36.398  38.418  18.840  1.00 38.21      B3
ATOM  2573  O   SER   365      37.103  38.989  19.662  1.00 36.91      B3
ATOM  2574  N   TYR   366      36.575  38.540  17.514  1.00 38.00      B3
ATOM  2575  H   TYR   366      36.079  37.945  16.910  1.00  0.00      B3
ATOM  2576  CA  TYR   366      37.568  39.463  16.969  1.00 39.85      B3
ATOM  2577  CB  TYR   366      37.776  39.330  15.436  1.00 38.53      B3
ATOM  2578  CG  TYR   366      38.662  40.447  14.879  1.00 38.21      B3
ATOM  2579  CD1 TYR   366      38.104  41.464  14.129  1.00 37.18      B3
ATOM  2580  CE1 TYR   366      38.918  42.495  13.678  1.00 41.77      B3
ATOM  2581  CD2 TYR   366      40.021  40.443  15.182  1.00 40.21      B3
ATOM  2582  CE2 TYR   366      40.849  41.466  14.739  1.00 40.76      B3
ATOM  2583  CZ  TYR   366      40.297  42.504  13.976  1.00 42.82      B3
ATOM  2584  OH  TYR   366      41.151  43.522  13.493  1.00 41.30      B3
ATOM  2585  HH  TYR   366      40.743  43.977  12.755  1.00  0.00      B3
ATOM  2586  C   TYR   366      37.133  40.893  17.241  1.00 40.55      B3
ATOM  2587  O   TYR   366      37.917  41.647  17.798  1.00 40.92      B3
ATOM  2588  N   ARG   367      35.933  41.309  16.853  1.00 41.88      B3
ATOM  2589  H   ARG   367      35.360  40.682  16.360  1.00  0.00      B3
ATOM  2590  CA  ARG   367      35.442  42.653  17.139  1.00 43.32      B3
ATOM  2591  CB  ARG   367      34.013  42.709  16.650  1.00 46.82      B3
ATOM  2592  CG  ARG   367      33.528  44.130  16.650  1.00 56.74      B3
ATOM  2593  CD  ARG   367      32.069  44.267  16.248  1.00 61.81      B3
ATOM  2594  NE  ARG   367      31.723  45.687  16.229  1.00 66.59      B3
ATOM  2595  HE  ARG   367      32.438  46.356  16.172  1.00  0.00      B3
ATOM  2596  CZ  ARG   367      30.458  46.091  16.308  1.00 69.75      B3
ATOM  2597  NH1 ARG   367      29.448  45.220  16.413  1.00 72.65      B3
ATOM  2598  HH11 ARG   367      29.631  44.236  16.410  1.00  0.00      B3
ATOM  2599  HH12 ARG   367      28.503  45.548  16.445  1.00  0.00      B3
ATOM  2600  NH2 ARG   367      30.160  47.375  16.162  1.00 71.64      B3
ATOM  2601  HH21 ARG   367      29.204  47.665  16.272  1.00  0.00      B3
ATOM  2602  HH22 ARG   367      30.888  48.043  16.013  1.00  0.00      B3
ATOM  2603  C   ARG   367      35.551  43.011  15.635  1.00 40.96      B3
ATOM  2604  O   ARG   367      35.994  44.090  19.012  1.00 41.30      B3
ATOM  2605  N   VAL   368      35.160  42.135  19.542  1.00 39.83      B3
ATOM  2606  H   VAL   368      34.726  41.316  19.217  1.00  0.00      B3
ATOM  2607  CA  VAL   368      35.331  42.292  20.968  1.00 37.34      B3
ATOM  2608  CB  VAL   368      34.748  41.043  21.664  1.00 35.75      B3
ATOM  2609  CG1 VAL   368      35.087  40.867  23.140  1.00 35.10      B3
ATOM  2610  CG2 VAL   368      33.259  41.230  21.586  1.00 33.28      B3
ATOM  2611  C   VAL   368      36.815  42.459  21.223  1.00 38.75      B3
ATOM  2612  O   VAL   368      37.144  43.498  21.772  1.00 40.11      B3
ATOM  2613  N   LEU   369      37.759  41.600  20.845  1.00 39.59      B3
ATOM  2614  H   LEU   369      37.492  40.818  20.308  1.00  0.00      B3
ATOM  2615  CA  LEU   369      39.180  41.780  21.148  1.00 40.05      B3
ATOM  2616  CB  LEU   369      39.984  40.601  20.679  1.00 37.15      B3
ATOM  2617  CG  LEU   369      39.831  39.335  21.426  1.00 37.54      B3
ATOM  2618  CD1 LEU   369      40.349  38.238  20.528  1.00 39.70      B3
ATOM  2619  CD2 LEU   369      40.563  39.394  22.747  1.00 36.86      B3
ATOM  2620  C   LEU   369      39.817  43.031  20.542  1.00 41.88      B3
ATOM  2621  O   LEU   369      40.711  43.654  21.144  1.00 41.30      B3
ATOM  2622  N   ARG   370      39.333  43.413  19.354  1.00 42.80      B3
ATOM  2623  H   ARG   370      38.619  42.884  18.957  1.00  0.00      B3
ATOM  2624  CA  ARG   370      39.819  44.577  18.663  1.00 43.96      B3
ATOM  2625  CB  ARG   370      39.184  44.569  17.316  1.00 42.06      B3
ATOM  2626  CG  ARG   370      39.424  45.719  16.371  1.00 43.94      B3
ATOM  2627  CD  ARG   370      40.894  45.910  16.169  1.00 45.37      B3
ATOM  2628  NE  ARG   370      41.219  46.681  14.976  1.00 48.00      B3
ATOM  2629  HE  ARG   370      40.524  46.867  14.312  1.00  0.00      B3
ATOM  2630  CZ  ARG   370      42.469  47.153  14.791  1.00 48.45      B3
ATOM  2631  NH1 ARG   370      43.443  46.961  15.691  1.00 49.13      B3
ATOM  2632  HH11 ARG   370      43.262  46.456  16.534  1.00  0.00      B3
ATOM  2633  HH12 ARG   370      44.357  47.326  15.520  1.00  0.00      B3
ATOM  2634  NH2 ARG   370      42.821  47.710  13.635  1.00 47.59      B3
ATOM  2635  HH21 ARG   370      42.163  47.785  12.889  1.00  0.00      B3
ATOM  2636  HH22 ARG   370      43.751  48.057  13.516  1.00  0.00      B3
ATOM  2637  C   ARG   370      39.386  45.740  19.558  1.00 49.12      B3
ATOM  2638  O   ARG   370      40.216  46.615  19.826  1.00 49.67      B3
ATOM  2639  N   HIS   371      38.162  45.728  20.123  1.00 52.30      B3
ATOM  2640  H   HIS   371      37.581  44.955  19.949  1.00  0.00      B3
ATOM  2641  CA  HIS   371      37.745  46.738  21.080  1.00 56.65      B3
ATOM  2642  CB  HIS   371      36.284  46.604  21.459  1.00 62.15      B3
ATOM  2643  CG  HIS   371      35.320  46.991  20.346  1.00 71.70      B3
ATOM  2644  CD2 HIS   371      35.596  47.877  19.313  1.00 75.03      B3
ATOM  2645  ND1 HIS   371      34.067  46.546  20.166  1.00 75.91      B3
ATOM  2646  HD1 HIS   371      33.594  45.897  20.732  1.00  0.00      B3
ATOM  2647  CE1 HIS   371      33.580  47.116  19.077  1.00 77.30      B3
ATOM  2648  NE2 HIS   371      34.507  47.914  18.573  1.00 77.52      B3
ATOM  2649  HE2 HIS   371      34.401  48.460  17.764  1.00  0.00      B3
ATOM  2650  C   HIS   371      38.533  46.669  22.382  1.00 56.97      B3
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EP 0 612 846 A1

FIGURE 5

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ATOM  2651  O   HIS   371      38.458  47.592  23.176  1.00 58.12      B3
ATOM  2652  N   LEU   372      39.271  45.632  22.715  1.00 56.98      B3
ATOM  2653  H   LEU   372      39.302  44.855  22.122  1.00  0.00      B3
ATOM  2654  CA  LEU   372      40.048  45.597  23.939  1.00 57.77      B3
ATOM  2655  CB  LEU   372      39.725  44.272  24.633  1.00 57.29      B3
ATOM  2656  CG  LEU   372      38.566  44.144  25.611  1.00 55.87      B3
ATOM  2657  CD1 LEU   372      37.358  44.892  25.123  1.00 55.77      B3
ATOM  2658  CD2 LEU   372      38.211  42.675  25.749  1.00 55.33      B3
ATOM  2659  C   LEU   372      41.554  45.755  23.647  1.00 58.81      B3
ATOM  2660  O   LEU   372      42.447  45.475  24.476  1.00 59.12      B3
ATOM  2661  N   ALA   373      41.942  46.168  22.447  1.00 59.27      B3
ATOM  2662  H   ALA   373      41.271  46.255  21.731  1.00  0.00      B3
ATOM  2663  CA  ALA   373      43.336  46.425  22.147  1.00 60.03      B3
ATOM  2664  CB  ALA   373      43.755  45.485  21.021  1.00 59.87      B3
ATOM  2665  C   ALA   373      43.616  47.895  21.762  1.00 61.22      B3
ATOM  2666  OT1 ALA   373      44.798  48.243  21.697  1.00 62.45      B3
ATOM  2667  OT2 ALA   373      42.682  48.700  21.583  1.00 61.55      B3
ATOM  2668  CB  LEU   410      23.866  49.243   1.118  1.00 53.10      C1
ATOM  2669  CG  LEU   410      23.982  47.812   0.738  1.00 51.85      C1
ATOM  2670  CD1 LEU   410      25.074  47.596  -0.330  1.00 52.64      C1
ATOM  2671  CD2 LEU   410      24.125  47.081   2.058  1.00 49.28      C1
ATOM  2672  C   LEU   410      22.381  51.214   1.635  1.00 52.99      C1
ATOM  2673  O   LEU   410      22.242  52.166   0.845  1.00 53.00      C1
ATOM  2674  HT1 LEU   410      22.721  50.836  -0.665  1.00  0.00      C1
ATOM  2675  HT2 LEU   410      21.194  50.178  -0.557  1.00  0.00      C1
ATOM  2676  N   LEU   410      22.198  49.968  -0.415  1.00 54.31      C1
ATOM  2677  HT3 LEU   410      22.529  49.174  -0.998  1.00  0.00      C1
ATOM  2678  CA  LEU   410      22.478  49.815   1.004  1.00 53.64      C1
ATOM  2679  N   PRO   411      22.450  51.433   2.965  1.00 52.95      C1
ATOM  2680  CD  PRO   411      22.466  50.407   4.022  1.00 52.54      C1
ATOM  2681  CA  PRO   411      22.666  52.766   3.548  1.00 53.25      C1
ATOM  2682  CB  PRO   411      22.688  52.541   5.068  1.00 52.85      C1
ATOM  2683  CG  PRO   411      23.163  51.108   5.203  1.00 52.83      C1
ATOM  2684  C   PRO   411      23.958  53.413   3.023  1.00 53.47      C1
ATOM  2685  O   PRO   411      25.073  52.878   3.167  1.00 54.02      C1
ATOM  2686  N   GLN   412      23.787  54.599   2.411  1.00 52.79      C1
ATOM  2687  H   GLN   412      22.863  54.900   2.294  1.00  0.00      C1
ATOM  2688  CA  GLN   412      24.873  55.413   1.871  1.00 50.44      C1
ATOM  2689  CB  GLN   412      24.387  56.762   1.413  1.00 52.47      C1
ATOM  2690  CG  GLN   412      25.364  57.408   0.437  1.00 56.51      C1
ATOM  2691  CD  GLN   412      25.228  56.954  -1.017  1.00 59.40      C1
ATOM  2692  OE1 GLN   412      25.869  57.506  -1.913  1.00 59.67      C1
ATOM  2693  NE2 GLN   412      24.336  56.022  -1.389  1.00 60.12      C1
ATOM  2694 HE21 GLN   412      23.734  55.616  -0.737  1.00  0.00      C1
ATOM  2695 HE22 GLN   412      24.396  55.748  -2.328  1.00  0.00      C1
ATOM  2696  C   GLN   412      25.930  55.646   2.916  1.00 48.22      C1
ATOM  2697  O   GLN   412      27.089  55.591   2.545  1.00 46.78      C1
ATOM  2698  N   SER   413      25.614  55.842   4.201  1.00 47.90      C1
ATOM  2699  H   SER   413      24.693  55.976   4.492  1.00  0.00      C1
ATOM  2700  CA  SER   413      26.696  55.984   5.144  1.00 48.75      C1
ATOM  2701  CB  SER   413      26.261  56.344   6.548  1.00 50.61      C1
ATOM  2702  OG  SER   413      27.378  56.872   7.301  1.00 53.05      C1
ATOM  2703  HG  SER   413      28.178  56.355   7.145  1.00  0.00      C1
ATOM  2704  C   SER   413      27.480  54.684   5.267  1.00 48.71      C1
ATOM  2705  O   SER   413      28.698  54.839   5.392  1.00 50.77      C1
ATOM  2706  N   PHE   414      26.947  53.440   5.208  1.00 46.01      C1
ATOM  2707  H   PHE   414      25.996  53.323   5.015  1.00  0.00      C1
ATOM  2708  CA  PHE   414      27.787  52.233   5.274  1.00 42.92      C1
ATOM  2709  CB  PHE   414      26.959  50.915   5.232  1.00 40.76      C1
ATOM  2710  CG  PHE   414      27.633  49.627   4.757  1.00 35.06      C1
ATOM  2711  CD1 PHE   414      27.583  49.256   3.425  1.00 34.71      C1
ATOM  2712  CD2 PHE   414      28.262  48.800   5.663  1.00 34.81      C1
ATOM  2713  CE1 PHE   414      28.156  48.056   3.014  1.00 26.16      C1
ATOM  2714  CE2 PHE   414      28.832  47.602   5.247  1.00 33.40      C1
ATOM  2715  CZ  PHE   414      28.781  47.223   3.923  1.00 34.22      C1
ATOM  2716  C   PHE   414      28.667  52.271   4.044  1.00 41.25      C1
ATOM  2717  O   PHE   414      29.831  51.902   4.110  1.00 41.47      C1
ATOM  2718  N   LEU   415      28.122  52.748   2.942  1.00 39.50      C1
ATOM  2719  H   LEU   415      27.188  53.044   2.946  1.00  0.00      C1
ATOM  2720  CA  LEU   415      28.865  52.769   1.721  1.00 39.91      C1
ATOM  2721  CB  LEU   415      27.946  53.205   0.641  1.00 41.98      C1
ATOM  2722  CG  LEU   415      27.903  52.274  -0.526  1.00 44.75      C1
ATOM  2723  CD1 LEU   415      26.430  51.951  -0.780  1.00 42.93      C1
ATOM  2724  CD2 LEU   415      28.793  52.853  -1.648  1.00 45.91      C1
ATOM  2725  C   LEU   415      30.081  53.669   1.755  1.00 40.03      C1
ATOM  2726  O   LEU   415      31.142  53.348   1.183  1.00 46.28      C1
ATOM  2727  N   LEU   416      29.901  54.779   2.487  1.00 37.46      C1
ATOM  2728  H   LEU   416      29.028  54.948   2.899  1.00  0.00      C1
ATOM  2729  CA  LEU   416      30.942  55.756   2.602  1.00 34.05      C1
ATOM  2730  CB  LEU   416      30.294  57.089   2.998  1.00 34.67      C1
ATOM  2731  CG  LEU   416      29.438  57.704   1.851  1.00 35.24      C1
ATOM  2732  CD1 LEU   416      28.770  58.948   2.358  1.00 31.67      C1
ATOM  2733  CD2 LEU   416      30.310  57.948   0.593  1.00 35.50      C1
ATOM  2734  C   LEU   416      31.952  55.258   3.586  1.00 31.97      C1
ATOM  2735  O   LEU   416      33.131  55.427   3.270  1.00 33.32      C1
ATOM  2736  N   ALA   417      31.573  54.619   4.695  1.00 29.05      C1
ATOM  2737  H   ALA   417      30.621  54.616   4.927  1.00  0.00      C1
ATOM  2738  CA  ALA   417      32.524  53.882   5.561  1.00 29.64      C1
ATOM  2739  CB  ALA   417      31.853  53.087   6.680  1.00 25.16      C1
ATOM  2740  C   ALA   417      33.319  52.827   4.777  1.00 30.68      C1
ATOM  2741  O   ALA   417      34.536  52.721   4.877  1.00 31.52      C1
ATOM  2742  N   CYS   418      32.726  52.041   3.905  1.00 32.19      C1
ATOM  2743  H   CYS   418      31.748  52.017   3.866  1.00  0.00      C1
ATOM  2744  CA  CYS   418      33.499  51.119   3.103  1.00 33.67      C1
ATOM  2745  CB  CYS   418      32.657  50.250   2.226  1.00 33.85      C1
ATOM  2746  SG  CYS   418      31.623  49.208   3.246  1.00 37.80      C1
ATOM  2747  C   CYS   418      34.446  51.818   2.170  1.00 34.80      C1
ATOM  2748  O   CYS   418      35.626  51.441   2.173  1.00 36.47      C1
ATOM  2749  N   LEU   419      34.009  52.820   1.377  1.00 35.09      C1
ATOM  2750  H   LEU   419      33.082  53.131   1.460  1.00  0.00      C1
ATOM  2751  CA  LEU   419      34.886  53.446   0.375  1.00 34.14      C1
ATOM  2752  CB  LEU   419      34.062  54.484  -0.413  1.00 37.09      C1
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FIGURE 5

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ATOM  2753 CG  LEU  419      32.866  53.853  -1.244  1.00 39.61      C1
ATOM  2754 CD1 LEU  419      31.866  54.918  -1.609  1.00 39.24      C1
ATOM  2755 CD2 LEU  419      33.349  53.207  -2.553  1.00 40.02      C1
ATOM  2756 C   LEU  419      36.102  54.041   1.047  1.00 32.33      C1
ATOM  2757 O   LEU  419      37.198  53.973   0.549  1.00 31.60      C1
ATOM  2758 N   GLU  420      35.974  54.483   2.273  1.00 31.92      C1
ATOM  2759 H   GLU  420      35.068  54.528   2.648  1.00  0.00      C1
ATOM  2760 CA  GLU  420      37.078  54.905   3.092  1.00 31.79      C1
ATOM  2761 CB  GLU  420      36.477  55.462   4.344  1.00 34.29      C1
ATOM  2762 CG  GLU  420      37.430  56.240   5.185  1.00 38.66      C1
ATOM  2763 CD  GLU  420      36.952  56.499   6.609  1.00 45.20      C1
ATOM  2764 OE1 GLU  420      37.873  56.849   7.367  1.00 45.67      C1
ATOM  2765 OE2 GLU  420      35.745  56.345   6.954  1.00 44.21      C1
ATOM  2766 C   GLU  420      38.043  53.763   3.423  1.00 31.87      C1
ATOM  2767 O   GLU  420      39.253  53.949   3.270  1.00 32.82      C1
ATOM  2768 N   GLN  421      37.553  52.624   3.954  1.00 30.46      C1
ATOM  2769 H   GLN  421      36.583  52.556   4.098  1.00  0.00      C1
ATOM  2770 CA  GLN  421      38.366  51.461   4.283  1.00 29.34      C1
ATOM  2771 CB  GLN  421      37.545  50.389   4.984  1.00 30.88      C1
ATOM  2772 CG  GLN  421      37.308  50.634   6.463  1.00 33.58      C1
ATOM  2773 CD  GLN  421      36.320  49.625   7.058  1.00 37.89      C1
ATOM  2774 OE1 GLN  421      35.357  49.236   6.398  1.00 43.18      C1
ATOM  2775 NE2 GLN  421      36.427  49.095   8.275  1.00 37.13      C1
ATOM  2776 HE21 GLN  421      35.695  48.505   8.556  1.00  0.00      C1
ATOM  2777 HE22 GLN  421      37.207  49.330   8.812  1.00  0.00      C1
ATOM  2778 C   GLN  421      38.991  50.862   3.026  1.00 27.36      C1
ATOM  2779 O   GLN  421      40.152  50.445   3.099  1.00 29.09      C1
ATOM  2780 N   VAL  422      38.379  50.845   1.847  1.00 23.57      C1
ATOM  2781 H   VAL  422      37.448  51.138   1.803  1.00  0.00      C1
ATOM  2782 CA  VAL  422      39.077  50.420   0.651  1.00 23.52      C1
ATOM  2783 CB  VAL  422      38.163  50.636  -0.556  1.00 22.67      C1
ATOM  2784 CG1 VAL  422      38.873  50.455  -1.868  1.00 21.56      C1
ATOM  2785 CG2 VAL  422      37.057  49.610  -0.465  1.00 26.79      C1
ATOM  2786 C   VAL  422      40.353  51.254   0.514  1.00 26.22      C1
ATOM  2787 O   VAL  422      41.458  50.708   0.508  1.00 28.77      C1
ATOM  2788 N   ARG  423      40.275  52.599   0.575  1.00 27.49      C1
ATOM  2789 H   ARG  423      39.402  53.016   0.735  1.00  0.00      C1
ATOM  2790 CA  ARG  423      41.436  53.456   0.346  1.00 25.91      C1
ATOM  2791 CB  ARG  423      41.098  54.943   0.312  1.00 24.39      C1
ATOM  2792 CG  ARG  423      40.167  55.366  -0.807  1.00 22.81      C1
ATOM  2793 CD  ARG  423      40.525  54.798  -2.172  1.00 25.55      C1
ATOM  2794 NE  ARG  423      39.707  55.387  -3.216  1.00 25.38      C1
ATOM  2795 HE  ARG  423      39.168  56.173  -2.989  1.00  0.00      C1
ATOM  2796 CZ  ARG  423      39.629  54.928  -4.466  1.00 27.32      C1
ATOM  2797 NH1 ARG  423      40.264  53.857  -4.949  1.00 26.37      C1
ATOM  2798 HH11 ARG  423      40.884  53.341  -4.365  1.00  0.00      C1
ATOM  2799 HH12 ARG  423      40.150  53.595  -5.907  1.00  0.00      C1
ATOM  2800 NH2 ARG  423      38.960  55.682  -5.325  1.00 30.38      C1
ATOM  2801 HH21 ARG  423      38.539  56.537  -5.023  1.00  0.00      C1
ATOM  2802 HH22 ARG  423      38.865  55.385  -6.275  1.00  0.00      C1
ATOM  2803 C   ARG  423      42.429  53.241   1.432  1.00 23.60      C1
ATOM  2804 O   ARG  423      43.594  53.147   1.127  1.00 24.37      C1
ATOM  2805 N   LYS  424      42.065  53.050   2.668  1.00 24.38      C1
ATOM  2806 H   LYS  424      41.109  53.051   2.890  1.00  0.00      C1
ATOM  2807 CA  LYS  424      43.043  52.855   3.722  1.00 25.12      C1
ATOM  2808 CB  LYS  424      42.352  52.791   5.051  1.00 23.89      C1
ATOM  2809 CG  LYS  424      43.312  52.936   6.190  1.00 28.56      C1
ATOM  2810 CD  LYS  424      42.579  52.580   7.486  1.00 35.51      C1
ATOM  2811 CE  LYS  424      41.338  53.425   7.853  1.00 40.33      C1
ATOM  2812 NZ  LYS  424      40.519  52.722   8.834  1.00 42.23      C1
ATOM  2813 HZ1 LYS  424      41.079  52.559   9.695  1.00  0.00      C1
ATOM  2814 HZ2 LYS  424      40.208  51.814   8.435  1.00  0.00      C1
ATOM  2815 HZ3 LYS  424      39.689  53.306   9.065  1.00  0.00      C1
ATOM  2816 C   LYS  424      43.761  51.547   3.462  1.00 27.10      C1
ATOM  2817 O   LYS  424      44.923  51.425   3.848  1.00 30.64      C1
ATOM  2818 N   ILE  425      43.190  50.542   2.794  1.00 26.85      C1
ATOM  2819 H   ILE  425      42.260  50.607   2.488  1.00  0.00      C1
ATOM  2820 CA  ILE  425      43.949  49.312   2.561  1.00 25.16      C1
ATOM  2821 CB  ILE  425      42.965  48.093   2.336  1.00 24.91      C1
ATOM  2822 CG2 ILE  425      43.654  46.786   1.995  1.00 22.01      C1
ATOM  2823 CG1 ILE  425      42.229  47.909   3.633  1.00 25.34      C1
ATOM  2824 CD  ILE  425      40.885  47.169   3.432  1.00 25.68      C1
ATOM  2825 C   ILE  425      44.824  49.549   1.346  1.00 23.84      C1
ATOM  2826 O   ILE  425      45.959  49.069   1.316  1.00 24.57      C1
ATOM  2827 N   GLN  426      44.361  50.267   0.323  1.00 23.28      C1
ATOM  2828 H   GLN  426      43.451  50.630   0.393  1.00  0.00      C1
ATOM  2829 CA  GLN  426      45.164  50.531  -0.871  1.00 24.13      C1
ATOM  2830 CB  GLN  426      44.421  51.344  -1.896  1.00 24.04      C1
ATOM  2831 CG  GLN  426      43.275  50.539  -2.396  1.00 23.56      C1
ATOM  2832 CD  GLN  426      42.446  51.305  -3.511  1.00 23.92      C1
ATOM  2833 OE1 GLN  426      41.704  52.047  -3.345  1.00 25.34      C1
ATOM  2834 NE2 GLN  426      42.337  50.509  -4.672  1.00 27.55      C1
ATOM  2835 HE21 GLN  426      41.755  50.948  -5.323  1.00  0.00      C1
ATOM  2836 HE22 GLN  426      42.850  49.696  -4.851  1.00  0.00      C1
ATOM  2837 C   GLN  426      46.404  51.312  -0.488  1.00 26.09      C1
ATOM  2838 O   GLN  426      47.486  51.109  -1.046  1.00 29.73      C1
ATOM  2839 N   GLY  427      46.300  52.204   0.499  1.00 26.49      C1
ATOM  2840 H   GLY  427      45.410  52.414   0.854  1.00  0.00      C1
ATOM  2841 CA  GLY  427      47.446  52.894   1.022  1.00 24.25      C1
ATOM  2842 C   GLY  427      48.467  51.913   1.589  1.00 23.08      C1
ATOM  2843 O   GLY  427      49.597  51.921   1.106  1.00 22.28      C1
ATOM  2844 N   ASP  428      48.107  51.073   2.575  1.00 22.75      C1
ATOM  2845 H   ASP  428      47.189  51.111   2.918  1.00  0.00      C1
ATOM  2846 CA  ASP  428      49.039  50.108   3.131  1.00 23.87      C1
ATOM  2847 CB  ASP  428      48.415  49.199   4.117  1.00 26.52      C1
ATOM  2848 CG  ASP  428      47.437  49.779   5.097  1.00 28.84      C1
ATOM  2849 OD1 ASP  428      46.420  49.151   5.265  1.00 31.81      C1
ATOM  2850 OD2 ASP  428      47.662  50.804   5.716  1.00 30.77      C1
ATOM  2851 C   ASP  428      49.626  49.191   2.063  1.00 24.16      C1
ATOM  2852 O   ASP  428      50.812  48.896   2.088  1.00 26.17      C1
ATOM  2853 N   GLY  429      48.840  48.822   1.069  1.00 23.01      C1
ATOM  2854 H   GLY  429      47.905  49.113   1.071  1.00  0.00      C1
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FIGURE 5

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ATOM  2855 CA  GLY  429      49.289  47.964   0.029  1.00 25.44      C1
ATOM  2856 C   GLY  429      50.405  48.649  -0.716  1.00 27.39      C1
ATOM  2857 O   GLY  429      51.528  48.135  -0.741  1.00 28.51      C1
ATOM  2858 N   ALA  430      50.127  49.840  -1.271  1.00 28.26      C1
ATOM  2859 H   ALA  430      49.216  50.185  -1.172  1.00  0.00      C1
ATOM  2860 CA  ALA  430      51.094  50.643  -2.015  1.00 26.04      C1
ATOM  2861 CB  ALA  430      50.490  51.976  -2.407  1.00 27.93      C1
ATOM  2862 C   ALA  430      52.300  50.927  -1.133  1.00 25.19      C1
ATOM  2863 O   ALA  430      53.393  51.053  -1.655  1.00 25.43      C1
ATOM  2864 N   ALA  431      52.171  50.979   0.186  1.00 24.05      C1
ATOM  2865 H   ALA  431      51.279  50.872   0.579  1.00  0.00      C1
ATOM  2866 CA  ALA  431      53.295  51.213   1.035  1.00 26.29      C1
ATOM  2867 CB  ALA  431      52.874  51.522   2.458  1.00 24.14      C1
ATOM  2868 C   ALA  431      54.139  49.972   1.073  1.00 29.82      C1
ATOM  2869 O   ALA  431      55.360  50.085   0.959  1.00 31.97      C1
ATOM  2870 N   LEU  432      53.562  48.777   1.203  1.00 31.87      C1
ATOM  2871 H   LEU  432      52.585  48.726   1.279  1.00  0.00      C1
ATOM  2872 CA  LEU  432      54.337  47.540   1.165  1.00 33.92      C1
ATOM  2873 CB  LEU  432      53.430  46.315   1.301  1.00 37.42      C1
ATOM  2874 CG  LEU  432      54.063  44.952   1.574  1.00 37.40      C1
ATOM  2875 CD1 LEU  432      54.751  44.949   2.950  1.00 38.10      C1
ATOM  2876 CD2 LEU  432      52.966  43.901   1.492  1.00 36.27      C1
ATOM  2877 C   LEU  432      55.096  47.404  -0.146  1.00 33.74      C1
ATOM  2878 O   LEU  432      56.306  47.179  -0.138  1.00 33.29      C1
ATOM  2879 N   GLN  433      54.402  47.564  -1.276  1.00 34.57      C1
ATOM  2880 H   GLN  433      53.439  47.733  -1.186  1.00  0.00      C1
ATOM  2881 CA  GLN  433      55.002  47.526  -2.600  1.00 35.83      C1
ATOM  2882 CB  GLN  433      53.999  47.892  -3.664  1.00 35.52      C1
ATOM  2883 CG  GLN  433      52.996  46.823  -3.832  1.00 39.40      C1
ATOM  2884 CD  GLN  433      52.049  47.097  -4.973  1.00 42.46      C1
ATOM  2885 OE1 GLN  433      50.924  47.526  -4.786  1.00 48.22      C1
ATOM  2886 NE2 GLN  433      52.376  46.878  -6.225  1.00 44.77      C1
ATOM  2887 HE21 GLN  433      53.271  46.540  -6.433  1.00  0.00      C1
ATOM  2888 HE22 GLN  433      51.693  47.087  -6.892  1.00  0.00      C1
ATOM  2889 C   GLN  433      56.177  48.485  -2.757  1.00 36.48      C1
ATOM  2890 O   GLN  433      57.214  48.118  -3.312  1.00 38.08      C1
ATOM  2891 N   GLU  434      56.055  49.719  -2.287  1.00 36.11      C1
ATOM  2892 H   GLU  434      55.210  49.978  -1.854  1.00  0.00      C1
ATOM  2893 CA  GLU  434      57.089  50.719  -2.426  1.00 35.93      C1
ATOM  2894 CB  GLU  434      56.408  52.030  -2.068  1.00 41.28      C1
ATOM  2895 CG  GLU  434      57.126  53.356  -2.019  1.00 43.07      C1
ATOM  2896 CD  GLU  434      57.832  53.516  -0.698  1.00 45.70      C1
ATOM  2897 OE1 GLU  434      57.190  53.538   0.367  1.00 49.33      C1
ATOM  2898 OE2 GLU  434      59.051  53.579  -0.760  1.00 45.45      C1
ATOM  2899 C   GLU  434      58.257  50.348  -1.548  1.00 34.00      C1
ATOM  2900 O   GLU  434      59.388  50.481  -1.983  1.00 32.93      C1
ATOM  2901 N   LYS  435      58.067  49.860  -0.330  1.00 34.34      C1
ATOM  2902 H   LYS  435      57.146  49.837   0.014  1.00  0.00      C1
ATOM  2903 CA  LYS  435      59.151  49.358   0.511  1.00 34.56      C1
ATOM  2904 CB  LYS  435      58.577  49.010   1.847  1.00 33.89      C1
ATOM  2905 CG  LYS  435      58.357  50.231   2.709  1.00 36.71      C1
ATOM  2906 CD  LYS  435      58.244  49.748   4.137  1.00 40.31      C1
ATOM  2907 CE  LYS  435      58.293  50.861   5.213  1.00 45.32      C1
ATOM  2908 NZ  LYS  435      58.494  50.325   6.575  1.00 47.31      C1
ATOM  2909 HZ1 LYS  435      59.388  49.795   6.611  1.00  0.00      C1
ATOM  2910 HZ2 LYS  435      57.708  49.689   6.818  1.00  0.00      C1
ATOM  2911 HZ3 LYS  435      58.534  51.109   7.257  1.00  0.00      C1
ATOM  2912 C   LYS  435      59.906  48.135  -0.065  1.00 36.10      C1
ATOM  2913 O   LYS  435      61.139  48.036  -0.012  1.00 37.08      C1
ATOM  2914 N   LEU  436      59.215  47.168  -0.665  1.00 36.28      C1
ATOM  2915 H   LEU  436      58.235  47.245  -0.651  1.00  0.00      C1
ATOM  2916 CA  LEU  436      59.793  45.994  -1.304  1.00 34.25      C1
ATOM  2917 CB  LEU  436      58.655  45.076  -1.753  1.00 33.41      C1
ATOM  2918 CG  LEU  436      57.920  44.327  -0.610  1.00 34.72      C1
ATOM  2919 CD1 LEU  436      56.764  43.538  -1.181  1.00 33.50      C1
ATOM  2920 CD2 LEU  436      58.880  43.375   0.117  1.00 36.39      C1
ATOM  2921 C   LEU  436      60.669  46.383  -2.467  1.00 33.31      C1
ATOM  2922 O   LEU  436      61.756  45.825  -2.647  1.00 33.94      C1
ATOM  2923 N   CYS  437      60.220  47.374  -3.222  1.00 32.34      C1
ATOM  2924 H   CYS  437      59.290  47.661  -3.097  1.00  0.00      C1
ATOM  2925 CA  CYS  437      60.978  47.949  -4.301  1.00 32.01      C1
ATOM  2926 C   CYS  437      62.214  48.704  -3.857  1.00 34.70      C1
ATOM  2927 O   CYS  437      63.313  48.599  -4.412  1.00 36.26      C1
ATOM  2928 CB  CYS  437      60.094  48.840  -5.008  1.00 30.97      C1
ATOM  2929 SG  CYS  437      61.003  49.666  -6.319  1.00 36.22      C1
ATOM  2930 N   ALA  438      62.016  49.463  -2.785  1.00 36.35      C1
ATOM  2931 H   ALA  438      61.108  49.547  -2.431  1.00  0.00      C1
ATOM  2932 CA  ALA  438      63.060  50.226  -2.170  1.00 35.83      C1
ATOM  2933 CB  ALA  438      62.440  51.107  -1.153  1.00 36.38      C1
ATOM  2934 C   ALA  438      64.065  49.294  -1.527  1.00 37.01      C1
ATOM  2935 O   ALA  438      65.132  49.168  -2.092  1.00 39.39      C1
ATOM  2936 N   THR  439      63.808  48.591  -0.422  1.00 36.59      C1
ATOM  2937 H   THR  439      62.947  48.723   0.014  1.00  0.00      C1
ATOM  2938 CA  THR  439      64.742  47.669   0.223  1.00 35.70      C1
ATOM  2939 CB  THR  439      64.073  47.042   1.400  1.00 35.34      C1
ATOM  2940 OG1 THR  439      63.323  48.048   2.040  1.00 38.31      C1
ATOM  2941 HG1 THR  439      62.419  47.999   1.706  1.00  0.00      C1
ATOM  2942 CG2 THR  439      65.039  46.479   2.369  1.00 36.50      C1
ATOM  2943 C   THR  439      65.331  46.517  -0.590  1.00 36.10      C1
ATOM  2944 O   THR  439      66.448  46.093  -0.312  1.00 36.51      C1
ATOM  2945 N   TYR  440      64.603  45.917  -1.548  1.00 36.02      C1
ATOM  2946 H   TYR  440      63.751  46.319  -1.822  1.00  0.00      C1
ATOM  2947 CA  TYR  440      65.057  44.691  -2.198  1.00 34.28      C1
ATOM  2948 CB  TYR  440      64.175  43.480  -1.878  1.00 33.99      C1
ATOM  2949 CG  TYR  440      64.016  43.240  -0.397  1.00 34.14      C1
ATOM  2950 CD1 TYR  440      62.773  43.230   0.169  1.00 35.16      C1
ATOM  2951 CE1 TYR  440      62.625  43.037   1.532  1.00 36.66      C1
ATOM  2952 CD2 TYR  440      65.126  43.064   0.385  1.00 37.83      C1
ATOM  2953 CE2 TYR  440      64.992  42.881   1.752  1.00 39.02      C1
ATOM  2954 CZ  TYR  440      63.741  42.864   2.317  1.00 37.34      C1
ATOM  2955 OH  TYR  440      63.637  42.649   3.678  1.00 37.56      C1
ATOM  2956 HH  TYR  440      64.498  42.343   3.988  1.00  0.00      C1
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FIGURE 5

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ATOM  2957 C   TYR  440     65.088  44.768  -3.681  1.00 34.07      C1
ATOM  2958 O   TYR  440     65.598  43.823  -4.267  1.00 35.54      C1
ATOM  2959 N   LYS  441     64.627  45.833  -4.330  1.00 33.18      C1
ATOM  2960 H   LYS  441     64.345  46.623  -3.822  1.00  0.00      C1
ATOM  2961 CA  LYS  441     64.595  45.957  -5.763  1.00 30.44      C1
ATOM  2962 CB  LYS  441     65.983  45.759  -6.364  1.00 33.76      C1
ATOM  2963 CG  LYS  441     66.729  47.080  -6.407  1.00 39.59      C1
ATOM  2964 CD  LYS  441     67.273  47.497  -5.045  1.00 47.69      C1
ATOM  2965 CE  LYS  441     67.503  49.028  -4.984  1.00 53.37      C1
ATOM  2966 NZ  LYS  441     66.267  49.780  -5.240  1.00 57.64      C1
ATOM  2967 HZ1 LYS  441     65.568  49.549  -4.506  1.00  0.00      C1
ATOM  2968 HZ2 LYS  441     65.885  49.525  -6.173  1.00  0.00      C1
ATOM  2969 HZ3 LYS  441     66.468  50.801  -5.219  1.00  0.00      C1
ATOM  2970 C   LYS  441     63.629  45.015  -6.425  1.00 28.86      C1
ATOM  2971 O   LYS  441     63.791  44.688  -7.603  1.00 29.95      C1
ATOM  2972 N   LEU  442     62.556  44.601  -5.749  1.00 27.58      C1
ATOM  2973 H   LEU  442     62.392  44.924  -4.837  1.00  0.00      C1
ATOM  2974 CA  LEU  442     61.554  43.780  -6.402  1.00 28.82      C1
ATOM  2975 CB  LEU  442     60.947  42.694  -5.466  1.00 26.98      C1
ATOM  2976 CG  LEU  442     61.905  41.634  -4.847  1.00 27.75      C1
ATOM  2977 CD1 LEU  442     61.133  40.643  -4.009  1.00 24.29      C1
ATOM  2978 CD2 LEU  442     62.667  40.932  -5.963  1.00 19.72      C1
ATOM  2979 C   LEU  442     60.575  44.892  -6.635  1.00 30.59      C1
ATOM  2980 O   LEU  442     59.811  45.261  -5.741  1.00 32.36      C1
ATOM  2981 N   CYS  443     60.700  45.506  -7.804  1.00 32.15      C1
ATOM  2982 H   CYS  443     61.423  45.199  -8.389  1.00  0.00      C1
ATOM  2983 CA  CYS  443     59.866  46.645  -8.191  1.00 32.69      C1
ATOM  2984 C   CYS  443     58.807  46.380  -9.217  1.00 33.43      C1
ATOM  2985 O   CYS  443     58.051  47.288  -9.465  1.00 34.10      C1
ATOM  2986 CB  CYS  443     60.715  47.800  -8.743  1.00 30.74      C1
ATOM  2987 SG  CYS  443     61.938  48.345  -7.519  1.00 32.96      C1
ATOM  2988 N   HIS  444     58.649  45.260  -9.911  1.00 35.65      C1
ATOM  2989 H   HIS  444     59.147  44.445  -9.659  1.00  0.00      C1
ATOM  2990 CA  HIS  444     57.662  45.172 -10.975  1.00 37.75      C1
ATOM  2991 CB  HIS  444     58.329  45.224 -12.330  1.00 37.09      C1
ATOM  2992 CG  HIS  444     59.149  46.476 -12.560  1.00 41.36      C1
ATOM  2993 CD2 HIS  444     60.434  46.664 -12.075  1.00 41.40      C1
ATOM  2994 ND1 HIS  444     58.811  47.563 -13.261  1.00 41.74      C1
ATOM  2995 HD1 HIS  444     57.892  47.890 -13.410  1.00  0.00      C1
ATOM  2996 CE1 HIS  444     59.850  48.372 -13.217  1.00 42.00      C1
ATOM  2997 NE2 HIS  444     60.817  47.832 -12.502  1.00 41.38      C1
ATOM  2998 HE2 HIS  444     61.690  48.248 -12.334  1.00  0.00      C1
ATOM  2999 C   HIS  444     56.889  43.871 -10.878  1.00 40.10      C1
ATOM  3000 O   HIS  444     57.461  42.867 -11.309  1.00 40.15      C1
ATOM  3001 N   PRO  445     55.615  43.752 -10.406  1.00 42.06      C1
ATOM  3002 CD  PRO  445     54.738  44.836  -9.937  1.00 41.56      C1
ATOM  3003 CA  PRO  445     54.913  42.497 -10.276  1.00 40.90      C1
ATOM  3004 CB  PRO  445     53.569  42.882  -9.730  1.00 39.35      C1
ATOM  3005 CG  PRO  445     53.364  44.274 -10.215  1.00 39.35      C1
ATOM  3006 C   PRO  445     54.868  41.782 -11.600  1.00 42.18      C1
ATOM  3007 O   PRO  445     54.769  40.571 -11.569  1.00 45.69      C1
ATOM  3008 N   GLU  446     55.082  42.380 -12.769  1.00 41.64      C1
ATOM  3009 H   GLU  446     55.320  43.320 -12.761  1.00  0.00      C1
ATOM  3010 CA  GLU  446     55.025  41.656 -14.029  1.00 42.05      C1
ATOM  3011 CB  GLU  446     54.967  42.639 -15.183  1.00 47.06      C1
ATOM  3012 CG  GLU  446     54.109  43.925 -14.992  1.00 56.71      C1
ATOM  3013 CD  GLU  446     54.728  45.083 -14.162  1.00 62.28      C1
ATOM  3014 OE1 GLU  446     54.100  45.472 -13.178  1.00 66.26      C1
ATOM  3015 OE2 GLU  446     55.818  45.604 -14.473  1.00 65.55      C1
ATOM  3016 C   GLU  446     56.237  40.722 -14.197  1.00 40.44      C1
ATOM  3017 O   GLU  446     56.186  39.708 -14.904  1.00 41.66      C1
ATOM  3018 N   GLU  447     57.360  40.995 -13.538  1.00 37.89      C1
ATOM  3019 H   GLU  447     57.394  41.809 -12.999  1.00  0.00      C1
ATOM  3020 CA  GLU  447     58.519  40.096 -13.509  1.00 36.73      C1
ATOM  3021 CB  GLU  447     59.750  40.810 -12.976  1.00 34.60      C1
ATOM  3022 CG  GLU  447     60.320  41.883 -13.850  1.00 35.27      C1
ATOM  3023 CD  GLU  447     61.450  42.699 -13.197  1.00 36.14      C1
ATOM  3024 OE1 GLU  447     62.240  43.286 -13.939  1.00 37.31      C1
ATOM  3025 OE2 GLU  447     61.541  42.782 -11.970  1.00 32.80      C1
ATOM  3026 C   GLU  447     58.311  38.850 -12.599  1.00 36.31      C1
ATOM  3027 O   GLU  447     59.113  37.911 -12.592  1.00 36.33      C1
ATOM  3028 N   LEU  448     57.273  38.765 -11.769  1.00 33.81      C1
ATOM  3029 H   LEU  448     56.554  39.431 -11.802  1.00  0.00      C1
ATOM  3030 CA  LEU  448     57.145  37.691 -10.839  1.00 31.88      C1
ATOM  3031 CB  LEU  448     57.080  38.299  -9.484  1.00 29.29      C1
ATOM  3032 CG  LEU  448     58.008  39.432  -9.140  1.00 29.81      C1
ATOM  3033 CD1 LEU  448     57.907  39.863  -7.684  1.00 26.02      C1
ATOM  3034 CD2 LEU  448     59.396  38.931  -9.392  1.00 31.13      C1
ATOM  3035 C   LEU  448     55.863  36.977 -11.165  1.00 33.75      C1
ATOM  3036 O   LEU  448     55.436  36.145 -10.382  1.00 33.96      C1
ATOM  3037 N   VAL  449     55.166  37.233 -12.263  1.00 36.99      C1
ATOM  3038 H   VAL  449     55.580  37.800 -12.942  1.00  0.00      C1
ATOM  3039 CA  VAL  449     53.819  36.701 -12.472  1.00 41.46      C1
ATOM  3040 CB  VAL  449     53.157  37.546 -13.625  1.00 41.56      C1
ATOM  3041 CG1 VAL  449     54.002  37.614 -14.880  1.00 42.22      C1
ATOM  3042 CG2 VAL  449     51.921  36.858 -14.112  1.00 42.01      C1
ATOM  3043 C   VAL  449     53.760  35.192 -12.733  1.00 44.81      C1
ATOM  3044 O   VAL  449     52.866  34.469 -12.227  1.00 44.54      C1
ATOM  3045 N   LEU  450     54.716  34.669 -13.515  1.00 47.21      C1
ATOM  3046 H   LEU  450     55.416  35.260 -13.870  1.00  0.00      C1
ATOM  3047 CA  LEU  450     54.771  33.243 -13.781  1.00 50.57      C1
ATOM  3048 CB  LEU  450     55.942  32.894 -14.628  1.00 50.75      C1
ATOM  3049 CG  LEU  450     56.148  33.488 -15.994  1.00 52.39      C1
ATOM  3050 CD1 LEU  450     57.152  32.586 -16.673  1.00 53.05      C1
ATOM  3051 CD2 LEU  450     54.882  33.534 -16.833  1.00 54.10      C1
ATOM  3052 C   LEU  450     54.911  32.468 -12.471  1.00 53.84      C1
ATOM  3053 O   LEU  450     54.297  31.406 -12.266  1.00 55.62      C1
ATOM  3054 N   LEU  451     55.685  33.097 -11.575  1.00 55.46      C1
ATOM  3055 H   LEU  451     56.073  33.954 -11.849  1.00  0.00      C1
ATOM  3056 CA  LEU  451     55.998  32.654 -10.223  1.00 56.01      C1
ATOM  3057 CB  LEU  451     57.137  33.542  -9.731  1.00 55.80      C1
ATOM  3058 CG  LEU  451     57.745  33.278  -8.394  1.00 56.96      C1
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FIGURE 5

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ATOM 3059 CD1 LEU 451     58.833 32.284 -8.653 1.00 59.12     C1
ATOM 3060 CD2 LEU 451     58.369 34.511 -7.751 1.00 58.27     C1
ATOM 3061 C  LEU 451      54.785 32.700 -9.280 1.00 55.96     C1
ATOM 3062 O  LEU 451      54.717 31.935 -8.319 1.00 53.74     C1
ATOM 3063 N  GLY 452      53.774 33.533 -9.522 1.00 57.52     C1
ATOM 3064 H  GLY 452      53.889 34.241 -10.191 1.00 0.00     C1
ATOM 3065 CA GLY 452      52.567 33.515 -8.710 1.00 60.66     C1
ATOM 3066 C  GLY 452      51.942 32.137 -8.772 1.00 63.64     C1
ATOM 3067 O  GLY 452      51.476 31.593 -7.782 1.00 62.60     C1
ATOM 3068 N  HIS 453      52.089 31.545 -9.969 1.00 68.46     C1
ATOM 3069 H  HIS 453      52.628 32.040 -10.618 1.00 0.00     C1
ATOM 3070 CA HIS 453      51.606 30.205 -10.326 1.00 72.27     C1
ATOM 3071 CB HIS 453      51.785 29.908 -11.828 1.00 73.84     C1
ATOM 3072 CG HIS 453      51.421 31.061 -12.777 1.00 77.81     C1
ATOM 3073 CD2 HIS 453     50.599 32.148 -12.498 1.00 79.29     C1
ATOM 3074 ND1 HIS 453     51.886 31.244 -14.012 1.00 79.84     C1
ATOM 3075 HD1 HIS 453     52.617 30.739 -14.425 1.00 0.00     C1
ATOM 3076 CE1 HIS 453     51.385 32.382 -14.470 1.00 81.11     C1
ATOM 3077 NE2 HIS 453     50.613 32.923 -13.551 1.00 79.85     C1
ATOM 3078 HE2 HIS 453     50.230 33.825 -13.586 1.00 0.00     C1
ATOM 3079 C  HIS 453      52.454 29.235 -9.515 1.00 73.43     C1
ATOM 3080 O  HIS 453      51.875 28.531 -8.692 1.00 73.56     C1
ATOM 3081 N  SER 454      53.785 29.207 -9.651 1.00 74.64     C1
ATOM 3082 H  SER 454      54.214 29.739 -10.351 1.00 0.00     C1
ATOM 3083 CA SER 454      54.639 28.411 -8.765 1.00 77.07     C1
ATOM 3084 CB SER 454      56.123 28.762 -8.980 1.00 77.34     C1
ATOM 3085 OG SER 454      57.095 27.715 -9.124 1.00 75.28     C1
ATOM 3086 HG SER 454      57.149 27.211 -8.306 1.00 0.00     C1
ATOM 3087 C  SER 454      54.332 28.608 -7.262 1.00 78.84     C1
ATOM 3088 O  SER 454      54.270 27.617 -6.535 1.00 80.57     C1
ATOM 3089 N  LEU 455      54.070 29.789 -6.693 1.00 79.72     C1
ATOM 3090 H  LEU 455      53.956 30.582 -7.250 1.00 0.00     C1
ATOM 3091 CA LEU 455      53.849 29.915 -5.257 1.00 80.43     C1
ATOM 3092 CB LEU 455      54.085 31.347 -4.838 1.00 80.20     C1
ATOM 3093 CG LEU 455      55.389 31.981 -5.269 1.00 81.67     C1
ATOM 3094 CD1 LEU 455     55.254 33.494 -5.419 1.00 81.36     C1
ATOM 3095 CD2 LEU 455     56.431 31.579 -4.264 1.00 82.26     C1
ATOM 3096 C  LEU 455      52.438 29.510 -4.848 1.00 81.56     C1
ATOM 3097 O  LEU 455      52.038 29.893 -3.741 1.00 82.22     C1
ATOM 3098 N  GLY 456      51.653 28.816 -5.708 1.00 81.89     C1
ATOM 3099 H  GLY 456      52.026 28.592 -6.584 1.00 0.00     C1
ATOM 3100 CA GLY 456      50.269 28.361 -5.467 1.00 82.22     C1
ATOM 3101 C  GLY 456      49.220 29.386 -4.973 1.00 82.56     C1
ATOM 3102 O  GLY 456      48.268 28.989 -4.276 1.00 82.38     C1
ATOM 3103 N  ILE 457      49.342 30.697 -5.286 1.00 82.54     C1
ATOM 3104 H  ILE 457      50.075 30.942 -5.894 1.00 0.00     C1
ATOM 3105 CA ILE 457      48.435 31.761 -4.824 1.00 81.63     C1
ATOM 3106 CB ILE 457      49.110 33.157 -5.086 1.00 80.69     C1
ATOM 3107 CG2 ILE 457     48.218 34.305 -4.662 1.00 79.76     C1
ATOM 3108 CG1 ILE 457     50.369 33.275 -4.253 1.00 79.82     C1
ATOM 3109 CD  ILE 457     51.506 33.868 -5.081 1.00 77.89     C1
ATOM 3110 C  ILE 457      47.048 31.698 -5.472 1.00 81.70     C1
ATOM 3111 O  ILE 457      46.903 31.761 -6.700 1.00 82.57     C1
ATOM 3112 N  PRO 458      45.963 31.583 -4.705 1.00 81.40     C1
ATOM 3113 CD PRO 458      45.959 31.225 -3.278 1.00 81.21     C1
ATOM 3114 CA PRO 458      44.607 31.643 -5.264 1.00 80.74     C1
ATOM 3115 CB PRO 458      43.779 30.942 -4.157 1.00 81.12     C1
ATOM 3116 CG PRO 458      44.757 30.293 -3.173 1.00 80.47     C1
ATOM 3117 C  PRO 458      44.120 33.063 -5.648 1.00 79.70     C1
ATOM 3118 O  PRO 458      43.674 33.736 -4.718 1.00 80.10     C1
ATOM 3119 N  TRP 459      44.171 33.662 -6.861 1.00 78.19     C1
ATOM 3120 H  TRP 459      44.614 33.185 -7.591 1.00 0.00     C1
ATOM 3121 CA TRP 459      43.543 34.986 -7.092 1.00 77.73     C1
ATOM 3122 CB TRP 459      43.802 35.428 -8.522 1.00 78.71     C1
ATOM 3123 CG TRP 459      43.054 36.677 -9.017 1.00 81.37     C1
ATOM 3124 CD2 TRP 459     41.802 36.771 -9.618 1.00 82.89     C1
ATOM 3125 CE2 TRP 459     41.717 38.139 -9.883 1.00 84.21     C1
ATOM 3126 CE3 TRP 459     40.738 35.960 -9.983 1.00 84.28     C1
ATOM 3127 CD1 TRP 459     43.661 37.899 -8.925 1.00 83.89     C1
ATOM 3128 NE1 TRP 459     42.828 38.765 -9.460 1.00 85.23     C1
ATOM 3129 HE1 TRP 459     42.944 39.738 -9.483 1.00 0.00     C1
ATOM 3130 CZ2 TRP 459     40.615 38.727 -10.494 1.00 84.17     C1
ATOM 3131 CZ3 TRP 459     39.630 36.538 -10.597 1.00 84.56     C1
ATOM 3132 CH2 TRP 459     39.562 37.904 -10.852 1.00 84.83     C1
ATOM 3133 C  TRP 459      42.009 35.013 -6.827 1.00 77.31     C1
ATOM 3134 O  TRP 459      41.202 34.244 -7.376 1.00 76.38     C1
ATOM 3135 N  ALA 460      41.557 35.969 -6.020 1.00 76.81     C1
ATOM 3136 H  ALA 460      42.187 36.640 -5.689 1.00 0.00     C1
ATOM 3137 CA ALA 460      40.158 36.044 -5.613 1.00 76.44     C1
ATOM 3138 CB ALA 460      40.072 36.724 -4.243 1.00 75.51     C1
ATOM 3139 C  ALA 460      39.237 36.764 -6.598 1.00 76.29     C1
ATOM 3140 O  ALA 460      39.449 37.976 -6.833 1.00 76.98     C1
ATOM 3141 N  PRO 461      38.217 36.147 -7.187 1.00 76.26     C1
ATOM 3142 CD PRO 461      38.104 34.684 -7.245 1.00 75.88     C1
ATOM 3143 CA PRO 461      37.242 36.793 -8.068 1.00 75.46     C1
ATOM 3144 CB PRO 461      36.605 35.605 -8.755 1.00 75.71     C1
ATOM 3145 CG PRO 461      36.703 34.458 -7.767 1.00 75.60     C1
ATOM 3146 C  PRO 461      36.221 37.803 -7.545 1.00 75.72     C1
ATOM 3147 O  PRO 461      35.677 37.734 -6.440 1.00 73.66     C1
ATOM 3148 N  LEU 462      35.996 38.767 -8.449 1.00 77.19     C1
ATOM 3149 H  LEU 462      36.516 38.723 -9.277 1.00 0.00     C1
ATOM 3150 CA LEU 462      35.069 39.891 -8.275 1.00 78.87     C1
ATOM 3151 CB LEU 462      35.674 40.984 -7.360 1.00 78.32     C1
ATOM 3152 CG LEU 462      34.786 41.959 -6.558 1.00 78.09     C1
ATOM 3153 CD1 LEU 462     34.051 42.987 -7.406 1.00 78.32     C1
ATOM 3154 CD2 LEU 462     33.767 41.092 -5.828 1.00 78.62     C1
ATOM 3155 C  LEU 462      34.701 40.565 -9.611 1.00 80.64     C1
ATOM 3156 OT1 LEU 462     33.507 40.842 -9.808 1.00 81.74     C1
ATOM 3157 OT2 LEU 462     35.606 40.847 -10.417 1.00 81.39     C1
ATOM 3158 CB  LEU 472     22.074 42.654 -1.426 1.00 62.24     C2
ATOM 3159 CG  LEU 472     22.278 44.145 -1.189 1.00 59.98     C2
ATOM 3160 CD1 LEU 472     23.496 44.325 -0.328 1.00 59.14     C2
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FIGURE 5

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ATOM 3161 CD2 LEU 472 22.501 44.883 -2.486 1.00 56.85 C2
ATOM 3162 C LEU 472 23.504 40.625 -1.996 1.00 63.91 C2
ATOM 3163 O LEU 472 23.738 39.874 -2.949 1.00 64.90 C2
ATOM 3164 1HT1 LEU 472 21.563 41.441 -3.595 1.00 0.00 C2
ATOM 3165 1HT2 LEU 472 23.091 41.291 -4.237 1.00 0.00 C2
ATOM 3166 N LEU 472 22.472 41.930 -3.693 1.00 64.29 C2
ATOM 3167 1HT3 LEU 472 22.358 42.849 -4.160 1.00 0.00 C2
ATOM 3168 CA LEU 472 23.092 42.037 -2.386 1.00 63.85 C2
ATOM 3169 N ALA 473 23.652 40.229 -0.733 1.00 63.02 C2
ATOM 3170 H ALA 473 23.533 40.867 0.002 1.00 0.00 C2
ATOM 3171 CA ALA 473 24.023 38.881 -0.353 1.00 62.37 C2
ATOM 3172 CB ALA 473 22.870 37.939 -0.558 1.00 63.65 C2
ATOM 3173 C ALA 473 25.196 38.354 -1.126 1.00 62.01 C2
ATOM 3174 O ALA 473 26.301 38.651 -0.715 1.00 63.36 C2
ATOM 3175 N GLY 474 25.032 37.784 -2.306 1.00 61.43 C2
ATOM 3176 H GLY 474 24.148 37.818 -2.722 1.00 0.00 C2
ATOM 3177 CA GLY 474 26.101 37.137 -3.047 1.00 63.80 C2
ATOM 3178 C GLY 474 27.354 37.950 -3.356 1.00 65.13 C2
ATOM 3179 O GLY 474 28.482 37.417 -3.257 1.00 66.24 C2
ATOM 3180 N CYS 475 27.175 39.237 -3.757 1.00 64.88 C2
ATOM 3181 H CYS 475 26.261 39.550 -3.885 1.00 0.00 C2
ATOM 3182 CA CYS 475 28.308 40.127 -4.068 1.00 61.84 C2
ATOM 3183 CB CYS 475 27.925 41.413 -4.806 1.00 63.74 C2
ATOM 3184 SG CYS 475 29.494 42.075 -5.437 1.00 68.86 C2
ATOM 3185 C CYS 475 28.995 40.567 -2.795 1.00 57.30 C2
ATOM 3186 O CYS 475 30.214 40.449 -2.724 1.00 57.14 C2
ATOM 3187 N LEU 476 28.230 40.983 -1.779 1.00 53.29 C2
ATOM 3188 H LEU 476 27.264 41.024 -1.885 1.00 0.00 C2
ATOM 3189 CA LEU 476 28.797 41.315 -0.493 1.00 50.43 C2
ATOM 3190 CB LEU 476 27.719 41.723 0.523 1.00 45.68 C2
ATOM 3191 CG LEU 476 27.130 43.165 0.497 1.00 42.80 C2
ATOM 3192 CD1 LEU 476 26.670 43.559 1.896 1.00 36.25 C2
ATOM 3193 CD2 LEU 476 28.180 44.180 0.057 1.00 40.22 C2
ATOM 3194 C LEU 476 29.546 40.108 0.042 1.00 50.42 C2
ATOM 3195 O LEU 476 30.614 40.222 0.646 1.00 50.61 C2
ATOM 3196 N SER 477 29.053 38.922 -0.270 1.00 50.62 C2
ATOM 3197 H SER 477 28.196 38.860 -0.729 1.00 0.00 C2
ATOM 3198 CA SER 477 29.721 37.712 0.125 1.00 51.41 C2
ATOM 3199 CB SER 477 28.778 36.524 -0.051 1.00 53.45 C2
ATOM 3200 OG SER 477 27.732 36.616 0.926 1.00 57.65 C2
ATOM 3201 HG SER 477 27.280 37.462 0.828 1.00 0.00 C2
ATOM 3202 C SER 477 30.978 37.525 -0.681 1.00 50.75 C2
ATOM 3203 O SER 477 31.980 37.143 -0.068 1.00 51.41 C2
ATOM 3204 N GLN 478 31.037 37.788 -1.984 1.00 50.21 C2
ATOM 3205 H GLN 478 30.222 38.056 -2.457 1.00 0.00 C2
ATOM 3206 CA GLN 478 32.307 37.697 -2.715 1.00 51.37 C2
ATOM 3207 CB GLN 478 32.064 37.929 -4.166 1.00 53.65 C2
ATOM 3208 CG GLN 478 31.983 36.570 -4.788 1.00 57.32 C2
ATOM 3209 CD GLN 478 31.354 36.649 -6.160 1.00 60.47 C2
ATOM 3210 OE1 GLN 478 31.999 36.504 -7.205 1.00 62.26 C2
ATOM 3211 NE2 GLN 478 30.045 36.878 -6.167 1.00 62.16 C2
ATOM 3212 1HE2 GLN 478 29.569 36.972 -5.317 1.00 0.00 C2
ATOM 3213 2HE2 GLN 478 29.641 36.928 -7.054 1.00 0.00 C2
ATOM 3214 C GLN 478 33.398 38.670 -2.249 1.00 50.66 C2
ATOM 3215 O GLN 478 34.584 38.314 -2.217 1.00 50.13 C2
ATOM 3216 N LEU 479 33.045 39.909 -1.859 1.00 48.78 C2
ATOM 3217 H LEU 479 32.131 40.223 -2.039 1.00 0.00 C2
ATOM 3218 CA LEU 479 34.015 40.800 -1.235 1.00 45.87 C2
ATOM 3219 CB LEU 479 33.434 42.141 -0.827 1.00 47.03 C2
ATOM 3220 CG LEU 479 32.853 43.083 -1.818 1.00 49.40 C2
ATOM 3221 CD1 LEU 479 32.596 44.393 -1.078 1.00 48.15 C2
ATOM 3222 CD2 LEU 479 33.779 43.258 -3.000 1.00 48.59 C2
ATOM 3223 C LEU 479 34.505 40.146 0.056 1.00 42.13 C2
ATOM 3224 O LEU 479 35.695 39.955 0.262 1.00 40.90 C2
ATOM 3225 N HIS 480 33.609 39.766 0.950 1.00 39.56 C2
ATOM 3226 H HIS 480 32.658 39.935 0.763 1.00 0.00 C2
ATOM 3227 CA HIS 480 33.979 39.108 2.179 1.00 37.81 C2
ATOM 3228 CB HIS 480 32.742 38.714 2.922 1.00 34.29 C2
ATOM 3229 CG HIS 480 33.094 38.241 4.309 1.00 33.82 C2
ATOM 3230 CD2 HIS 480 33.123 36.932 4.709 1.00 33.44 C2
ATOM 3231 ND1 HIS 480 33.450 38.995 5.344 1.00 34.27 C2
ATOM 3232 HD1 HIS 480 33.505 39.976 5.362 1.00 0.00 C2
ATOM 3233 CE1 HIS 480 33.706 38.223 6.365 1.00 33.80 C2
ATOM 3234 NE2 HIS 480 33.504 36.986 5.965 1.00 37.12 C2
ATOM 3235 HE2 HIS 480 33.637 36.202 6.544 1.00 0.00 C2
ATOM 3236 C HIS 480 34.836 37.860 1.961 1.00 39.08 C2
ATOM 3237 O HIS 480 35.716 37.631 2.791 1.00 40.93 C2
ATOM 3238 N SER 481 34.615 37.029 0.935 1.00 39.24 C2
ATOM 3239 H SER 481 33.900 37.241 0.305 1.00 0.00 C2
ATOM 3240 CA SER 481 35.391 35.818 0.683 1.00 38.17 C2
ATOM 3241 CB SER 481 34.813 34.943 -0.420 1.00 40.42 C2
ATOM 3242 OG SER 481 33.454 34.597 -0.137 1.00 47.61 C2
ATOM 3243 HG SER 481 32.898 35.385 -0.162 1.00 0.00 C2
ATOM 3244 C SER 481 36.724 36.272 0.211 1.00 36.12 C2
ATOM 3245 O SER 481 37.692 35.793 0.765 1.00 36.23 C2
ATOM 3246 N GLY 482 36.786 37.206 -0.744 1.00 36.21 C2
ATOM 3247 H GLY 482 35.956 37.498 -1.168 1.00 0.00 C2
ATOM 3248 CA GLY 482 38.028 37.792 -1.266 1.00 36.50 C2
ATOM 3249 C GLY 482 38.958 38.296 -0.151 1.00 36.14 C2
ATOM 3250 O GLY 482 40.142 37.936 -0.055 1.00 36.65 C2
ATOM 3251 N LEU 483 38.381 39.084 0.750 1.00 34.64 C2
ATOM 3252 H LEU 483 37.445 39.326 0.608 1.00 0.00 C2
ATOM 3253 CA LEU 483 39.073 39.593 1.900 1.00 32.07 C2
ATOM 3254 CB LEU 483 38.134 40.442 2.731 1.00 31.17 C2
ATOM 3255 CG LEU 483 37.535 41.687 2.081 1.00 33.11 C2
ATOM 3256 CD1 LEU 483 36.757 42.411 3.156 1.00 30.82 C2
ATOM 3257 CD2 LEU 483 38.599 42.593 1.480 1.00 29.56 C2
ATOM 3258 C LEU 483 39.600 38.461 2.745 1.00 32.91 C2
ATOM 3259 O LEU 483 40.752 38.498 3.199 1.00 31.25 C2
ATOM 3260 N PHE 484 38.767 37.422 2.925 1.00 34.08 C2
ATOM 3261 H PHE 484 37.930 37.408 2.471 1.00 0.00 C2
ATOM 3262 CA PHE 484 39.105 36.298 3.783 1.00 34.60 C2
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FIGURE 5

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ATOM  3263 CB  PHE  484      37.975  35.300   3.925  1.00 37.46      C2
ATOM  3264 CG  PHE  484      38.268  34.183   4.897  1.00 40.86      C2
ATOM  3265 CD1 PHE  484      38.219  32.884   4.482  1.00 45.62      C2
ATOM  3266 CD2 PHE  484      38.528  34.445   6.210  1.00 43.62      C2
ATOM  3267 CE1 PHE  484      38.421  31.858   5.395  1.00 47.98      C2
ATOM  3268 CE2 PHE  484      38.731  33.427   7.119  1.00 46.78      C2
ATOM  3269 CZ  PHE  484      38.677  32.119   6.720  1.00 48.06      C2
ATOM  3270 C   PHE  484      40.245  35.602   3.113  1.00 33.92      C2
ATOM  3271 O   PHE  484      41.162  35.289   3.826  1.00 34.25      C2
ATOM  3272 N   LEU  485      40.326  35.413   1.799  1.00 32.75      C2
ATOM  3273 H   LEU  485      39.577  35.717   1.250  1.00  0.00      C2
ATOM  3274 CA  LEU  485      41.475  34.778   1.163  1.00 33.74      C2
ATOM  3275 CB  LEU  485      41.183  34.629  -0.305  1.00 35.35      C2
ATOM  3276 CG  LEU  485      42.101  33.962  -1.275  1.00 37.80      C2
ATOM  3277 CD1 LEU  485      41.181  33.404  -2.345  1.00 41.44      C2
ATOM  3278 CD2 LEU  485      43.125  34.903  -1.899  1.00 40.07      C2
ATOM  3279 C   LEU  485      42.740  35.585   1.376  1.00 33.95      C2
ATOM  3280 O   LEU  485      43.766  35.060   1.850  1.00 33.84      C2
ATOM  3281 N   TYR  486      42.609  36.885   1.034  1.00 33.67      C2
ATOM  3282 H   TYR  486      41.757  37.186   0.659  1.00  0.00      C2
ATOM  3283 CA  TYR  486      43.662  37.862   1.242  1.00 31.33      C2
ATOM  3284 CB  TYR  486      43.210  39.290   0.714  1.00 35.33      C2
ATOM  3285 CG  TYR  486      43.300  39.325  -0.825  1.00 33.37      C2
ATOM  3286 CD1 TYR  486      42.154  39.405  -1.579  1.00 32.79      C2
ATOM  3287 CE1 TYR  486      42.228  39.290  -2.944  1.00 33.73      C2
ATOM  3288 CD2 TYR  486      44.533  39.153  -1.445  1.00 34.59      C2
ATOM  3289 CE2 TYR  486      44.618  39.033  -2.818  1.00 34.63      C2
ATOM  3290 CZ  TYR  486      43.451  39.096  -3.562  1.00 35.58      C2
ATOM  3291 OH  TYR  486      43.484  38.880  -4.942  1.00 38.24      C2
ATOM  3292 HH  TYR  486      42.614  39.086  -5.306  1.00  0.00      C2
ATOM  3293 C   TYR  486      44.068  37.905   2.697  1.00 27.39      C2
ATOM  3294 O   TYR  486      45.258  38.007   2.942  1.00 26.06      C2
ATOM  3295 N   GLN  487      43.270  37.691   3.708  1.00 26.95      C2
ATOM  3296 H   GLN  487      42.315  37.545   3.565  1.00  0.00      C2
ATOM  3297 CA  GLN  487      43.835  37.646   5.031  1.00 28.33      C2
ATOM  3298 CB  GLN  487      42.690  37.578   6.050  1.00 32.66      C2
ATOM  3299 CG  GLN  487      43.092  37.979   7.485  1.00 37.50      C2
ATOM  3300 CD  GLN  487      43.966  39.252   7.469  1.00 40.54      C2
ATOM  3301 OE1 GLN  487      43.441  40.346   7.292  1.00 40.45      C2
ATOM  3302 NE2 GLN  487      45.305  39.206   7.549  1.00 38.19      C2
ATOM  3303 HE21 GLN  487      45.755  40.057   7.452  1.00  0.00      C2
ATOM  3304 HE22 GLN  487      45.736  38.340   7.702  1.00  0.00      C2
ATOM  3305 C   GLN  487      44.791  36.455   5.207  1.00 28.53      C2
ATOM  3306 O   GLN  487      45.774  36.542   5.964  1.00 28.72      C2
ATOM  3307 N   GLY  488      44.550  35.363   4.454  1.00 28.32      C2
ATOM  3308 H   GLY  488      43.799  35.400   3.824  1.00  0.00      C2
ATOM  3309 CA  GLY  488      45.291  34.120   4.557  1.00 26.04      C2
ATOM  3310 C   GLY  488      46.660  34.264   4.033  1.00 25.75      C2
ATOM  3311 O   GLY  488      47.660  33.946   4.712  1.00 25.86      C2
ATOM  3312 N   LEU  489      46.655  34.798   2.818  1.00 25.05      C2
ATOM  3313 H   LEU  489      45.798  35.062   2.416  1.00  0.00      C2
ATOM  3314 CA  LEU  489      47.911  34.990   2.099  1.00 25.63      C2
ATOM  3315 CB  LEU  489      47.708  35.570   0.725  1.00 27.66      C2
ATOM  3316 CG  LEU  489      46.761  34.755  -0.189  1.00 30.83      C2
ATOM  3317 CD1 LEU  489      46.373  35.506  -1.471  1.00 30.43      C2
ATOM  3318 CD2 LEU  489      47.472  33.454  -0.502  1.00 32.62      C2
ATOM  3319 C   LEU  489      48.783  35.936   2.853  1.00 25.28      C2
ATOM  3320 O   LEU  489      49.973  35.705   2.914  1.00 27.37      C2
ATOM  3321 N   LEU  490      48.237  36.935   3.534  1.00 25.79      C2
ATOM  3322 H   LEU  490      47.267  37.079   3.515  1.00  0.00      C2
ATOM  3323 CA  LEU  490      49.072  37.868   4.220  1.00 25.96      C2
ATOM  3324 CB  LEU  490      48.274  39.139   4.567  1.00 27.96      C2
ATOM  3325 CG  LEU  490      47.823  40.131   3.474  1.00 27.89      C2
ATOM  3326 CD1 LEU  490      46.772  41.019   4.123  1.00 28.63      C2
ATOM  3327 CD2 LEU  490      48.988  40.942   2.899  1.00 28.15      C2
ATOM  3328 C   LEU  490      49.619  37.243   5.459  1.00 27.33      C2
ATOM  3329 O   LEU  490      50.740  37.528   5.865  1.00 26.73      C2
ATOM  3330 N   GLN  491      48.883  36.370   6.111  1.00 29.88      C2
ATOM  3331 H   GLN  491      47.984  36.127   5.799  1.00  0.00      C2
ATOM  3332 CA  GLN  491      49.430  35.809   7.314  1.00 33.01      C2
ATOM  3333 CB  GLN  491      48.305  35.113   8.027  1.00 38.68      C2
ATOM  3334 CG  GLN  491      47.856  35.963   9.197  1.00 46.07      C2
ATOM  3335 CD  GLN  491      46.348  36.262   9.278  1.00 50.83      C2
ATOM  3336 OE1 GLN  491      45.965  37.436   9.402  1.00 51.92      C2
ATOM  3337 NE2 GLN  491      45.425  35.294   9.278  1.00 51.67      C2
ATOM  3338 HE21 GLN  491      45.723  34.353   9.288  1.00  0.00      C2
ATOM  3339 HE22 GLN  491      44.489  35.560   9.286  1.00  0.00      C2
ATOM  3340 C   GLN  491      50.582  34.867   6.986  1.00 33.58      C2
ATOM  3341 O   GLN  491      51.582  34.828   7.715  1.00 34.65      C2
ATOM  3342 N   ALA  492      50.482  34.191   5.824  1.00 34.15      C2
ATOM  3343 H   ALA  492      49.701  34.382   5.264  1.00  0.00      C2
ATOM  3344 CA  ALA  492      51.416  33.177   5.321  1.00 33.64      C2
ATOM  3345 CB  ALA  492      50.818  32.500   4.081  1.00 31.67      C2
ATOM  3346 C   ALA  492      52.802  33.678   4.959  1.00 34.79      C2
ATOM  3347 O   ALA  492      53.789  32.943   4.879  1.00 36.03      C2
ATOM  3348 N   LEU  493      52.885  34.981   4.728  1.00 35.94      C2
ATOM  3349 H   LEU  493      52.060  35.510   4.721  1.00  0.00      C2
ATOM  3350 CA  LEU  493      54.139  35.634   4.426  1.00 34.86      C2
ATOM  3351 CB  LEU  493      53.898  36.990   3.747  1.00 31.36      C2
ATOM  3352 CG  LEU  493      53.127  37.065   2.443  1.00 28.27      C2
ATOM  3353 CD1 LEU  493      52.715  38.495   2.214  1.00 31.74      C2
ATOM  3354 CD2 LEU  493      53.977  36.608   1.285  1.00 28.79      C2
ATOM  3355 C   LEU  493      54.879  35.843   5.721  1.00 36.15      C2
ATOM  3356 O   LEU  493      55.985  36.374   5.694  1.00 36.70      C2
ATOM  3357 N   GLU  494      54.300  35.497   6.855  1.00 38.35      C2
ATOM  3358 H   GLU  494      53.395  35.130   6.836  1.00  0.00      C2
ATOM  3359 CA  GLU  494      54.910  35.648   8.157  1.00 41.14      C2
ATOM  3360 CB  GLU  494      55.621  34.340   8.545  1.00 46.61      C2
ATOM  3361 CG  GLU  494      54.711  33.471   9.419  1.00 53.71      C2
ATOM  3362 CD  GLU  494      54.195  32.160   8.785  1.00 60.27      C2
ATOM  3363 OE1 GLU  494      53.146  31.653   9.230  1.00 63.52      C2
ATOM  3364 OE2 GLU  494      54.839  31.630   7.862  1.00 62.76      C2
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FIGURE 5

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ATOM  3365 C   GLU  494     55.865  36.825   8.343  1.00 44.32      C2
ATOM  3366 O   GLU  494     57.055  36.678   8.610  1.00 46.91      C2
ATOM  3367 N   GLY  495     55.358  38.046   8.114  1.00 44.32      C2
ATOM  3368 H   GLY  495     54.450  38.112   7.753  1.00  0.00      C2
ATOM  3369 CA  GLY  495     56.104  39.272   8.368  1.00 42.36      C2
ATOM  3370 C   GLY  495     57.015  39.695   7.238  1.00 42.33      C2
ATOM  3371 O   GLY  495     57.397  40.866   7.220  1.00 42.42      C2
ATOM  3372 N   ILE  496     57.310  38.802   6.279  1.00 41.04      C2
ATOM  3373 H   ILE  496     56.927  37.906   6.374  1.00  0.00      C2
ATOM  3374 CA  ILE  496     58.259  38.993   5.192  1.00 41.15      C2
ATOM  3375 CB  ILE  496     57.929  40.216   4.253  1.00 38.60      C2
ATOM  3376 CG2 ILE  496     59.077  40.437   3.248  1.00 37.62      C2
ATOM  3377 CG1 ILE  496     56.662  39.964   3.480  1.00 36.39      C2
ATOM  3378 CD  ILE  496     56.314  41.071   2.470  1.00 35.27      C2
ATOM  3379 C   ILE  496     59.672  39.203   5.749  1.00 42.91      C2
ATOM  3380 O   ILE  496     60.541  38.396   5.448  1.00 44.22      C2
ATOM  3381 N   SER  497     59.998  40.228   6.533  1.00 44.31      C2
ATOM  3382 H   SER  497     59.297  40.852   6.827  1.00  0.00      C2
ATOM  3383 CA  SER  497     61.346  40.501   6.992  1.00 44.86      C2
ATOM  3384 CB  SER  497     62.204  41.254   5.938  1.00 44.13      C2
ATOM  3385 OG  SER  497     62.181  42.673   6.033  1.00 40.74      C2
ATOM  3386 HG  SER  497     62.531  42.964   5.170  1.00  0.00      C2
ATOM  3387 C   SER  497     61.164  41.413   8.185  1.00 45.85      C2
ATOM  3388 O   SER  497     60.132  42.110   8.288  1.00 47.55      C2
ATOM  3389 N   PRO  498     62.164  41.490   9.071  1.00 44.96      C2
ATOM  3390 CD  PRO  498     63.338  40.621   9.126  1.00 42.33      C2
ATOM  3391 CA  PRO  498     62.086  42.327  10.250  1.00 44.88      C2
ATOM  3392 CB  PRO  498     63.431  42.038  10.885  1.00 45.13      C2
ATOM  3393 CG  PRO  498     63.629  40.581  10.603  1.00 42.00      C2
ATOM  3394 C   PRO  498     61.760  43.799   9.983  1.00 45.22      C2
ATOM  3395 O   PRO  498     61.215  44.446  10.869  1.00 45.24      C2
ATOM  3396 N   GLU  499     62.017  44.314   8.777  1.00 46.16      C2
ATOM  3397 H   GLU  499     62.362  43.716   8.081  1.00  0.00      C2
ATOM  3398 CA  GLU  499     61.731  45.699   8.391  1.00 48.06      C2
ATOM  3399 CB  GLU  499     62.498  46.193   7.155  1.00 52.19      C2
ATOM  3400 CG  GLU  499     64.001  46.187   7.100  1.00 57.51      C2
ATOM  3401 CD  GLU  499     64.544  44.737   7.076  1.00 60.61      C2
ATOM  3402 OE1 GLU  499     64.755  44.231   8.162  1.00 62.96      C2
ATOM  3403 OE2 GLU  499     64.739  44.234   5.984  1.00 62.79      C2
ATOM  3404 C   GLU  499     60.269  45.896   7.981  1.00 46.94      C2
ATOM  3405 O   GLU  499     59.600  46.895   8.272  1.00 48.15      C2
ATOM  3406 N   LEU  500     59.806  44.934   7.193  1.00 44.38      C2
ATOM  3407 H   LEU  500     60.351  44.137   7.027  1.00  0.00      C2
ATOM  3408 CA  LEU  500     58.491  44.997   6.651  1.00 41.08      C2
ATOM  3409 CB  LEU  500     58.519  44.197   5.445  1.00 41.37      C2
ATOM  3410 CG  LEU  500     59.303  44.862   4.351  1.00 42.70      C2
ATOM  3411 CD1 LEU  500     59.776  43.828   3.351  1.00 43.98      C2
ATOM  3412 CD2 LEU  500     58.427  45.874   3.671  1.00 45.04      C2
ATOM  3413 C   LEU  500     57.455  44.521   7.628  1.00 40.59      C2
ATOM  3414 O   LEU  500     56.274  44.835   7.463  1.00 40.69      C2
ATOM  3415 N   GLY  501     57.866  43.835   8.685  1.00 39.37      C2
ATOM  3416 H   GLY  501     58.808  43.579   8.730  1.00  0.00      C2
ATOM  3417 CA  GLY  501     56.974  43.386   9.734  1.00 39.59      C2
ATOM  3418 C   GLY  501     55.816  44.324  10.092  1.00 39.66      C2
ATOM  3419 O   GLY  501     54.661  44.034   9.777  1.00 40.66      C2
ATOM  3420 N   PRO  502     55.986  45.462  10.742  1.00 39.90      C2
ATOM  3421 CD  PRO  502     57.227  45.908  11.335  1.00 41.18      C2
ATOM  3422 CA  PRO  502     54.912  46.387  11.045  1.00 38.67      C2
ATOM  3423 CB  PRO  502     55.594  47.494  11.791  1.00 39.23      C2
ATOM  3424 CG  PRO  502     56.989  47.405  11.221  1.00 41.36      C2
ATOM  3425 C   PRO  502     54.158  46.849   9.817  1.00 37.54      C2
ATOM  3426 O   PRO  502     52.966  47.139   9.961  1.00 38.36      C2
ATOM  3427 N   THR  503     54.728  46.887   8.609  1.00 35.13      C2
ATOM  3428 H   THR  503     55.663  46.638   8.449  1.00  0.00      C2
ATOM  3429 CA  THR  503     53.940  47.283   7.462  1.00 35.09      C2
ATOM  3430 CB  THR  503     54.832  47.376   6.245  1.00 34.48      C2
ATOM  3431 OG1 THR  503     56.025  48.018   6.668  1.00 38.23      C2
ATOM  3432 HG1 THR  503     55.857  48.946   6.845  1.00  0.00      C2
ATOM  3433 CG2 THR  503     54.197  48.162   5.126  1.00 35.56      C2
ATOM  3434 C   THR  503     52.836  46.252   7.215  1.00 35.37      C2
ATOM  3435 O   THR  503     51.671  46.552   6.915  1.00 37.11      C2
ATOM  3436 N   LEU  504     53.218  44.996   7.380  1.00 34.02      C2
ATOM  3437 H   LEU  504     54.146  44.799   7.647  1.00  0.00      C2
ATOM  3438 CA  LEU  504     52.301  43.912   7.173  1.00 32.50      C2
ATOM  3439 CB  LEU  504     53.127  42.650   7.002  1.00 34.78      C2
ATOM  3440 CG  LEU  504     53.464  42.256   5.601  1.00 34.07      C2
ATOM  3441 CD1 LEU  504     54.163  40.977   5.667  1.00 37.97      C2
ATOM  3442 CD2 LEU  504     52.254  41.865   4.809  1.00 37.34      C2
ATOM  3443 C   LEU  504     51.324  43.821   8.328  1.00 29.54      C2
ATOM  3444 O   LEU  504     50.141  43.562   8.078  1.00 30.40      C2
ATOM  3445 N   ASP  505     51.736  44.106   9.551  1.00 26.09      C2
ATOM  3446 H   ASP  505     52.689  44.269   9.699  1.00  0.00      C2
ATOM  3447 CA  ASP  505     50.798  44.084  10.643  1.00 27.88      C2
ATOM  3448 CB  ASP  505     51.446  44.345  11.926  1.00 29.86      C2
ATOM  3449 CG  ASP  505     52.500  43.312  12.239  1.00 34.64      C2
ATOM  3450 OD1 ASP  505     52.663  42.298  11.534  1.00 41.04      C2
ATOM  3451 OD2 ASP  505     53.179  43.542  13.224  1.00 37.40      C2
ATOM  3452 C   ASP  505     49.661  45.060  10.568  1.00 28.61      C2
ATOM  3453 O   ASP  505     48.566  44.739  11.039  1.00 30.30      C2
ATOM  3454 N   THR  506     49.894  46.242  10.002  1.00 28.29      C2
ATOM  3455 H   THR  506     50.823  46.493   9.804  1.00  0.00      C2
ATOM  3456 CA  THR  506     48.860  47.225   9.731  1.00 25.74      C2
ATOM  3457 CB  THR  506     49.497  48.556   9.336  1.00 26.14      C2
ATOM  3458 OG1 THR  506     49.944  49.099  10.588  1.00 31.64      C2
ATOM  3459 HG1 THR  506     49.243  49.072  11.246  1.00  0.00      C2
ATOM  3460 CG2 THR  506     48.594  49.517   8.619  1.00 24.46      C2
ATOM  3461 C   THR  506     48.022  46.735   8.615  1.00 24.00      C2
ATOM  3462 O   THR  506     46.817  46.864   8.719  1.00 25.85      C2
ATOM  3463 N   LEU  507     48.554  46.196   7.525  1.00 23.51      C2
ATOM  3464 H   LEU  507     49.527  46.073   7.453  1.00  0.00      C2
ATOM  3465 CA  LEU  507     47.682  45.770   6.434  1.00 23.85      C2
ATOM  3466 CB  LEU  507     48.574  45.408   5.196  1.00 23.33      C2
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FIGURE 5

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ATOM  3467 CG  LEU  507     48.010  44.919   3.858  1.00 20.85      C2
ATOM  3468 CD1 LEU  507     46.771  45.650   3.455  1.00 24.13      C2
ATOM  3469 CD2 LEU  507     49.074  45.055   2.842  1.00 20.13      C2
ATOM  3470 C   LEU  507     46.766  44.640   6.880  1.00 24.09      C2
ATOM  3471 O   LEU  507     45.600  44.764   6.541  1.00 25.80      C2
ATOM  3472 N   GLN  508     47.152  43.618   7.661  1.00 24.01      C2
ATOM  3473 H   GLN  508     48.112  43.555   7.866  1.00  0.00      C2
ATOM  3474 CA  GLN  508     46.228  42.625   8.214  1.00 23.71      C2
ATOM  3475 CB  GLN  508     46.961  41.627   9.036  1.00 23.83      C2
ATOM  3476 CG  GLN  508     47.937  40.899   8.173  1.00 31.64      C2
ATOM  3477 CD  GLN  508     48.842  40.080   9.054  1.00 34.00      C2
ATOM  3478 OE1 GLN  508     50.031  40.346   9.161  1.00 38.32      C2
ATOM  3479 NE2 GLN  508     48.321  39.090   9.748  1.00 36.30      C2
ATOM  3480 HE21 GLN  508    47.373  38.880   9.639  1.00  0.00      C2
ATOM  3481 HE22 GLN  508    48.891  38.636  10.406  1.00  0.00      C2
ATOM  3482 C   GLN  508     45.105  43.123   9.111  1.00 24.24      C2
ATOM  3483 O   GLN  508     43.978  42.650   9.014  1.00 24.06      C2
ATOM  3484 N   LEU  509     45.375  44.019  10.090  1.00 26.07      C2
ATOM  3485 H   LEU  509     46.316  44.262  10.222  1.00  0.00      C2
ATOM  3486 CA  LEU  509     44.378  44.640  10.977  1.00 25.71      C2
ATOM  3487 CB  LEU  509     44.993  45.555  12.031  1.00 25.60      C2
ATOM  3488 CG  LEU  509     45.838  44.757  13.042  1.00 29.00      C2
ATOM  3489 CD1 LEU  509     46.658  45.705  13.886  1.00 28.93      C2
ATOM  3490 CD2 LEU  509     44.950  43.919  13.937  1.00 27.94      C2
ATOM  3491 C   LEU  509     43.465  45.471  10.130  1.00 25.17      C2
ATOM  3492 O   LEU  509     42.274  45.411  10.408  1.00 27.22      C2
ATOM  3493 N   ASP  510     43.899  46.208   9.101  1.00 23.77      C2
ATOM  3494 H   ASP  510     44.865  46.277   8.930  1.00  0.00      C2
ATOM  3495 CA  ASP  510     42.955  46.898   8.240  1.00 22.66      C2
ATOM  3496 CB  ASP  510     43.652  47.829   7.306  1.00 25.21      C2
ATOM  3497 CG  ASP  510     44.316  48.966   8.068  1.00 33.01      C2
ATOM  3498 OD1 ASP  510     45.178  49.621   7.477  1.00 34.28      C2
ATOM  3499 OD2 ASP  510     43.988  49.209   9.250  1.00 34.44      C2
ATOM  3500 C   ASP  510     42.104  45.980   7.398  1.00 23.72      C2
ATOM  3501 O   ASP  510     40.897  46.220   7.387  1.00 24.80      C2
ATOM  3502 N   VAL  511     42.632  44.984   6.659  1.00 22.38      C2
ATOM  3503 H   VAL  511     43.611  44.900   6.620  1.00  0.00      C2
ATOM  3504 CA  VAL  511     41.823  44.010   5.961  1.00 21.89      C2
ATOM  3505 CB  VAL  511     42.752  42.924   5.366  1.00 22.71      C2
ATOM  3506 CG1 VAL  511     41.954  41.756   4.792  1.00 20.43      C2
ATOM  3507 CG2 VAL  511     43.529  43.524   4.210  1.00 16.19      C2
ATOM  3508 C   VAL  511     40.827  43.403   6.960  1.00 21.92      C2
ATOM  3509 O   VAL  511     39.625  43.447   6.719  1.00 23.46      C2
ATOM  3510 N   ALA  512     41.258  43.017   8.163  1.00 20.49      C2
ATOM  3511 H   ALA  512     42.216  43.063   8.361  1.00  0.00      C2
ATOM  3512 CA  ALA  512     40.388  42.357   9.108  1.00 20.83      C2
ATOM  3513 CB  ALA  512     41.103  41.974  10.344  1.00 17.89      C2
ATOM  3514 C   ALA  512     39.250  43.205   9.550  1.00 23.89      C2
ATOM  3515 O   ALA  512     38.201  42.668   9.874  1.00 24.61      C2
ATOM  3516 N   ASP  513     39.417  44.539   9.544  1.00 25.96      C2
ATOM  3517 H   ASP  513     40.300  44.888   9.291  1.00  0.00      C2
ATOM  3518 CA  ASP  513     38.374  45.471   9.947  1.00 25.37      C2
ATOM  3519 CB  ASP  513     38.958  46.787  10.373  1.00 26.88      C2
ATOM  3520 CG  ASP  513     39.682  46.679  11.712  1.00 32.35      C2
ATOM  3521 OD1 ASP  513     40.371  47.644  12.058  1.00 35.06      C2
ATOM  3522 OD2 ASP  513     39.580  45.646  12.390  1.00 34.10      C2
ATOM  3523 C   ASP  513     37.392  45.730   8.846  1.00 24.95      C2
ATOM  3524 O   ASP  513     36.185  45.868   9.090  1.00 26.92      C2
ATOM  3525 N   PHE  514     37.867  45.739   7.634  1.00 22.88      C2
ATOM  3526 H   PHE  514     38.829  45.614   7.475  1.00  0.00      C2
ATOM  3527 CA  PHE  514     36.974  45.922   6.530  1.00 24.09      C2
ATOM  3528 CB  PHE  514     37.812  46.061   5.266  1.00 18.11      C2
ATOM  3529 CG  PHE  514     36.956  46.470   4.072  1.00 17.86      C2
ATOM  3530 CD1 PHE  514     35.715  47.089   4.245  1.00 15.18      C2
ATOM  3531 CD2 PHE  514     37.440  46.197   2.804  1.00 13.77      C2
ATOM  3532 CE1 PHE  514     34.983  47.419   3.130  1.00 14.53      C2
ATOM  3533 CE2 PHE  514     36.693  46.539   1.705  1.00 12.10      C2
ATOM  3534 CZ  PHE  514     35.468  47.146   1.868  1.00 10.68      C2
ATOM  3535 C   PHE  514     36.026  44.703   6.450  1.00 29.23      C2
ATOM  3536 O   PHE  514     34.788  44.828   6.350  1.00 29.80      C2
ATOM  3537 N   ALA  515     36.604  43.490   6.531  1.00 31.15      C2
ATOM  3538 H   ALA  515     37.581  43.450   6.639  1.00  0.00      C2
ATOM  3539 CA  ALA  515     35.839  42.260   6.416  1.00 32.36      C2
ATOM  3540 CB  ALA  515     36.851  41.126   6.402  1.00 32.35      C2
ATOM  3541 C   ALA  515     34.801  42.089   7.535  1.00 32.59      C2
ATOM  3542 O   ALA  515     33.676  41.609   7.331  1.00 32.63      C2
ATOM  3543 N   THR  516     35.164  42.457   8.735  1.00 33.01      C2
ATOM  3544 H   THR  516     36.117  42.578   8.935  1.00  0.00      C2
ATOM  3545 CA  THR  516     34.231  42.566   9.821  1.00 35.18      C2
ATOM  3546 CB  THR  516     35.016  43.018  10.988  1.00 35.40      C2
ATOM  3547 OG1 THR  516     35.685  41.818  11.336  1.00 42.65      C2
ATOM  3548 HG1 THR  516     36.505  41.713  10.816  1.00  0.00      C2
ATOM  3549 CG2 THR  516     34.262  43.672  12.097  1.00 35.56      C2
ATOM  3550 C   THR  516     33.140  43.554   9.482  1.00 37.62      C2
ATOM  3551 O   THR  516     32.005  43.315   9.857  1.00 40.37      C2
ATOM  3552 N   THR  517     33.387  44.666   8.802  1.00 38.61      C2
ATOM  3553 H   THR  517     34.291  44.850   8.469  1.00  0.00      C2
ATOM  3554 CA  THR  517     32.359  45.641   8.512  1.00 38.92      C2
ATOM  3555 CB  THR  517     33.123  46.903   7.962  1.00 40.46      C2
ATOM  3556 OG1 THR  517     33.832  47.429   9.103  1.00 43.22      C2
ATOM  3557 HG1 THR  517     34.536  46.815   9.335  1.00  0.00      C2
ATOM  3558 CG2 THR  517     32.232  47.926   7.253  1.00 39.90      C2
ATOM  3559 C   THR  517     31.343  45.012   7.551  1.00 38.30      C2
ATOM  3560 O   THR  517     30.137  45.125   7.811  1.00 38.69      C2
ATOM  3561 N   ILE  518     31.790  44.344   6.466  1.00 37.54      C2
ATOM  3562 H   ILE  518     32.756  44.386   6.297  1.00  0.00      C2
ATOM  3563 CA  ILE  518     30.923  43.646   5.510  1.00 36.10      C2
ATOM  3564 CB  ILE  518     31.699  42.912   4.439  1.00 33.81      C2
ATOM  3565 CG2 ILE  518     30.703  42.202   3.555  1.00 33.46      C2
ATOM  3566 CG1 ILE  518     32.623  43.842   3.699  1.00 32.91      C2
ATOM  3567 CD  ILE  518     32.019  44.700   2.596  1.00 34.89      C2
ATOM  3568 C   ILE  518     30.172  42.591   6.317  1.00 38.64      C2
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FIGURE 5

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ATOM  3569 O   ILE  518     28.938  42.545   6.205  1.00 39.93      C2
ATOM  3570 N   TRP  519     30.842  41.785   7.179  1.00 38.64      C2
ATOM  3571 H   TRP  519     31.785  41.959   7.361  1.00  0.00      C2
ATOM  3572 CA  TRP  519     30.144  40.784   7.945  1.00 38.15      C2
ATOM  3573 CB  TRP  519     31.124  40.083   8.780  1.00 38.52      C2
ATOM  3574 CG  TRP  519     30.493  38.793   9.255  1.00 42.26      C2
ATOM  3575 CD2 TRP  519     29.880  38.578  10.473  1.00 41.70      C2
ATOM  3576 CE2 TRP  519     29.437  37.278  10.335  1.00 41.69      C2
ATOM  3577 CE3 TRP  519     29.648  39.282  11.629  1.00 42.26      C2
ATOM  3578 CD1 TRP  519     30.448  37.695   8.419  1.00 42.92      C2
ATOM  3579 NE1 TRP  519     29.788  36.793   9.115  1.00 44.19      C2
ATOM  3580 HE1 TRP  519     29.485  35.935   8.741  1.00  0.00      C2
ATOM  3581 CZ2 TRP  519     28.753  36.671  11.360  1.00 41.91      C2
ATOM  3582 CZ3 TRP  519     28.964  38.666  12.652  1.00 41.77      C2
ATOM  3583 CH2 TRP  519     28.522  37.375  12.515  1.00 41.05      C2
ATOM  3584 C   TRP  519     29.027  41.368   8.815  1.00 39.33      C2
ATOM  3585 O   TRP  519     27.888  40.919   8.726  1.00 38.28      C2
ATOM  3586 N   GLN  520     29.264  42.375   9.650  1.00 41.86      C2
ATOM  3587 H   GLN  520     30.180  42.717   9.700  1.00  0.00      C2
ATOM  3588 CA  GLN  520     28.240  43.016  10.464  1.00 44.63      C2
ATOM  3589 CB  GLN  520     28.691  44.198  11.239  1.00 47.03      C2
ATOM  3590 CG  GLN  520     29.602  43.808  12.360  1.00 54.78      C2
ATOM  3591 CD  GLN  520     29.910  45.009  13.243  1.00 60.14      C2
ATOM  3592 OE1 GLN  520     28.988  45.566  13.854  1.00 61.62      C2
ATOM  3593 NE2 GLN  520     31.172  45.456  13.371  1.00 60.46      C2
ATOM  3594 HE21 GLN  520    31.289  46.260  13.910  1.00  0.00      C2
ATOM  3595 HE22 GLN  520    31.895  44.966  12.932  1.00  0.00      C2
ATOM  3596 C   GLN  520     27.141  43.577   9.621  1.00 46.28      C2
ATOM  3597 O   GLN  520     26.001  43.474  10.059  1.00 48.62      C2
ATOM  3598 N   GLN  521     27.362  44.145   8.442  1.00 46.99      C2
ATOM  3599 H   GLN  521     28.272  44.257   8.092  1.00  0.00      C2
ATOM  3600 CA  GLN  521     26.226  44.638   7.716  1.00 49.02      C2
ATOM  3601 CB  GLN  521     26.632  45.553   6.566  1.00 50.06      C2
ATOM  3602 CG  GLN  521     25.456  46.226   5.790  1.00 50.87      C2
ATOM  3603 CD  GLN  521     24.616  47.278   6.534  1.00 51.82      C2
ATOM  3604 OE1 GLN  521     24.864  47.694   7.671  1.00 52.47      C2
ATOM  3605 NE2 GLN  521     23.577  47.776   5.888  1.00 50.36      C2
ATOM  3606 HE21 GLN  521    23.392  47.455   4.987  1.00  0.00      C2
ATOM  3607 HE22 GLN  521    23.044  48.424   6.390  1.00  0.00      C2
ATOM  3608 C   GLN  521     25.454  43.446   7.155  1.00 50.15      C2
ATOM  3609 O   GLN  521     24.214  43.514   7.177  1.00 51.82      C2
ATOM  3610 N   MET  522     26.057  42.348   6.668  1.00 49.18      C2
ATOM  3611 H   MET  522     27.038  42.291   6.688  1.00  0.00      C2
ATOM  3612 CA  MET  522     25.280  41.227   6.171  1.00 48.22      C2
ATOM  3613 CB  MET  522     26.185  40.167   5.607  1.00 46.36      C2
ATOM  3614 CG  MET  522     26.942  40.661   4.412  1.00 44.32      C2
ATOM  3615 SD  MET  522     27.855  39.435   3.426  1.00 48.35      C2
ATOM  3616 CE  MET  522     28.795  38.447   4.565  1.00 42.80      C2
ATOM  3617 C   MET  522     24.453  40.642   7.316  1.00 50.14      C2
ATOM  3618 O   MET  522     23.380  40.124   7.038  1.00 50.60      C2
ATOM  3619 N   GLU  523     24.848  40.722   8.596  1.00 51.91      C2
ATOM  3620 H   GLU  523     25.766  41.031   8.769  1.00  0.00      C2
ATOM  3621 CA  GLU  523     24.027  40.313   9.718  1.00 54.53      C2
ATOM  3622 CB  GLU  523     24.654  40.486  11.081  1.00 54.60      C2
ATOM  3623 CG  GLU  523     25.732  39.525  11.498  1.00 57.05      C2
ATOM  3624 CD  GLU  523     25.386  38.150  10.888  1.00 61.72      C2
ATOM  3625 OE1 GLU  523     24.515  37.487  11.477  1.00 64.66      C2
ATOM  3626 OE2 GLU  523     25.979  37.773   9.872  1.00 63.19      C2
ATOM  3627 C   GLU  523     22.773  41.116   9.836  1.00 58.29      C2
ATOM  3628 O   GLU  523     21.688  40.538   9.850  1.00 59.32      C2
ATOM  3629 N   ALA  524     22.920  42.432   9.992  1.00 61.41      C2
ATOM  3630 H   ALA  524     23.834  42.798  10.024  1.00  0.00      C2
ATOM  3631 CA  ALA  524     21.815  43.360  10.076  1.00 63.58      C2
ATOM  3632 CB  ALA  524     22.382  44.768   9.992  1.00 64.11      C2
ATOM  3633 C   ALA  524     20.818  43.109   8.946  1.00 64.79      C2
ATOM  3634 O   ALA  524     19.655  42.824   9.206  1.00 65.69      C2
ATOM  3635 N   ALA  525     21.251  43.083   7.693  1.00 66.44      C2
ATOM  3636 H   ALA  525     22.196  43.283   7.516  1.00  0.00      C2
ATOM  3637 CA  ALA  525     20.371  42.789   6.574  1.00 68.58      C2
ATOM  3638 CB  ALA  525     21.117  43.044   5.288  1.00 67.42      C2
ATOM  3639 C   ALA  525     19.841  41.356   6.558  1.00 71.11      C2
ATOM  3640 O   ALA  525     19.116  40.946   5.651  1.00 71.65      C2
ATOM  3641 N   GLY  526     20.257  40.510   7.498  1.00 74.20      C2
ATOM  3642 H   GLY  526     21.019  40.780   8.043  1.00  0.00      C2
ATOM  3643 CA  GLY  526     19.728  39.157   7.653  1.00 76.50      C2
ATOM  3644 C   GLY  526     20.430  38.085   6.842  1.00 78.19      C2
ATOM  3645 O   GLY  526     20.174  36.910   7.094  1.00 79.05      C2
ATOM  3646 N   MET  527     21.388  38.433   5.970  1.00 80.23      C2
ATOM  3647 H   MET  527     21.759  39.337   6.075  1.00  0.00      C2
ATOM  3648 CA  MET  527     22.055  37.489   5.063  1.00 81.73      C2
ATOM  3649 CB  MET  527     22.771  38.256   3.928  1.00 81.72      C2
ATOM  3650 CG  MET  527     22.385  39.719   3.720  1.00 83.52      C2
ATOM  3651 SD  MET  527     23.364  40.523   2.436  1.00 87.64      C2
ATOM  3652 CE  MET  527     22.600  42.117   2.402  1.00 84.47      C2
ATOM  3653 C   MET  527     23.078  36.584   5.780  1.00 82.64      C2
ATOM  3654 OT1 MET  527     22.974  35.357   5.624  1.00 83.38      C2
ATOM  3655 OT2 MET  527     23.949  37.104   6.500  1.00 82.99      C2
ATOM  3656 CB  MET  538     47.224  28.531   2.401  1.00 77.43      C3
ATOM  3657 CG  MET  538     47.397  30.041   2.427  1.00 77.15      C3
ATOM  3658 SD  MET  538     46.205  30.708   3.604  1.00 79.03      C3
ATOM  3659 CE  MET  538     44.850  31.067   2.515  1.00 77.20      C3
ATOM  3660 C   MET  538     48.549  27.839   0.386  1.00 75.32      C3
ATOM  3661 O   MET  538     49.130  26.745   0.405  1.00 77.11      C3
ATOM  3662 HT1 MET  538     47.563  26.068   1.449  1.00  0.00      C3
ATOM  3663 HT2 MET  538     46.638  26.204   0.075  1.00  0.00      C3
ATOM  3664 N   MET  538     46.724  26.552   1.050  1.00 77.52      C3
ATOM  3665 HT3 MET  538     45.873  26.401   1.617  1.00  0.00      C3
ATOM  3666 CA  MET  538     47.153  27.940   0.995  1.00 76.57      C3
ATOM  3667 N   PRO  539     49.089  28.870  -0.224  1.00 72.65      C3
ATOM  3668 CD  PRO  539     48.346  29.821  -1.046  1.00 72.26      C3
ATOM  3669 CA  PRO  539     50.526  29.020  -0.349  1.00 70.34      C3
ATOM  3670 CB  PRO  539     50.677  30.365  -1.006  1.00 71.49      C3
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FIGURE 5

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ATOM  3671 CG  PRO  539      49.437  30.503  -1.837  1.00 71.52      C3
ATOM  3672 C   PRO  539      51.250  28.931   0.991  1.00 67.83      C3
ATOM  3673 O   PRO  539      50.666  29.294   2.029  1.00 68.05      C3
ATOM  3674 N   ALA  540      52.484  28.417   0.961  1.00 64.48      C3
ATOM  3675 H   ALA  540      52.858  28.098   0.111  1.00  0.00      C3
ATOM  3676 CA  ALA  540      53.389  28.498   2.112  1.00 61.83      C3
ATOM  3677 CB  ALA  540      54.004  27.200   2.619  1.00 63.57      C3
ATOM  3678 C   ALA  540      54.559  29.212   1.496  1.00 58.74      C3
ATOM  3679 O   ALA  540      54.835  29.036   0.301  1.00 58.30      C3
ATOM  3680 N   PHE  541      55.256  30.008   2.292  1.00 55.25      C3
ATOM  3681 H   PHE  541      55.093  30.068   3.257  1.00  0.00      C3
ATOM  3682 CA  PHE  541      56.299  30.814   1.702  1.00 51.38      C3
ATOM  3683 CB  PHE  541      55.964  32.306   1.942  1.00 48.80      C3
ATOM  3684 CG  PHE  541      54.789  32.703   1.058  1.00 45.77      C3
ATOM  3685 CD1 PHE  541      54.992  32.939  -0.279  1.00 44.20      C3
ATOM  3686 CD2 PHE  541      53.507  32.747   1.582  1.00 44.76      C3
ATOM  3687 CE1 PHE  541      53.901  33.207  -1.074  1.00 43.98      C3
ATOM  3688 CE2 PHE  541      52.428  33.018   0.769  1.00 42.86      C3
ATOM  3689 CZ  PHE  541      52.625  33.247  -0.563  1.00 42.52      C3
ATOM  3690 C   PHE  541      57.586  30.364   2.333  1.00 49.80      C3
ATOM  3691 O   PHE  541      58.002  30.807   3.395  1.00 49.55      C3
ATOM  3692 N   ALA  542      58.172  29.442   1.562  1.00 48.21      C3
ATOM  3693 H   ALA  542      57.825  29.298   0.656  1.00  0.00      C3
ATOM  3694 CA  ALA  542      59.326  28.711   1.968  1.00 45.37      C3
ATOM  3695 CB  ALA  542      59.700  27.749   0.898  1.00 45.21      C3
ATOM  3696 C   ALA  542      60.510  29.567   2.266  1.00 44.87      C3
ATOM  3697 O   ALA  542      61.001  29.504   3.374  1.00 46.49      C3
ATOM  3698 N   SER  543      61.013  30.408   1.395  1.00 42.63      C3
ATOM  3699 H   SER  543      60.477  30.685   0.630  1.00  0.00      C3
ATOM  3700 CA  SER  543      62.253  31.108   1.708  1.00 40.31      C3
ATOM  3701 CB  SER  543      63.170  30.861   0.587  1.00 37.74      C3
ATOM  3702 OG  SER  543      62.391  31.181  -0.554  1.00 35.74      C3
ATOM  3703 HG  SER  543      61.824  30.423  -0.751  1.00  0.00      C3
ATOM  3704 C   SER  543      62.087  32.613   1.896  1.00 40.88      C3
ATOM  3705 O   SER  543      61.016  33.115   1.536  1.00 42.63      C3
ATOM  3706 N   ALA  544      63.120  33.383   2.310  1.00 38.84      C3
ATOM  3707 H   ALA  544      63.929  32.951   2.650  1.00  0.00      C3
ATOM  3708 CA  ALA  544      63.035  34.836   2.345  1.00 37.31      C3
ATOM  3709 CB  ALA  544      64.340  35.450   2.808  1.00 35.74      C3
ATOM  3710 C   ALA  544      62.723  35.372   0.947  1.00 37.06      C3
ATOM  3711 O   ALA  544      61.829  36.220   0.820  1.00 38.23      C3
ATOM  3712 N   PHE  545      63.357  34.881  -0.130  1.00 35.72      C3
ATOM  3713 H   PHE  545      64.131  34.298  -0.010  1.00  0.00      C3
ATOM  3714 CA  PHE  545      62.992  35.268  -1.484  1.00 33.66      C3
ATOM  3715 CB  PHE  545      63.738  34.534  -2.593  1.00 29.71      C3
ATOM  3716 CG  PHE  545      63.140  34.742  -3.990  1.00 29.62      C3
ATOM  3717 CD1 PHE  545      62.317  33.788  -4.557  1.00 29.80      C3
ATOM  3718 CD2 PHE  545      63.371  35.915  -4.689  1.00 31.90      C3
ATOM  3719 CE1 PHE  545      61.723  33.984  -5.795  1.00 28.61      C3
ATOM  3720 CE2 PHE  545      62.777  36.113  -5.928  1.00 31.00      C3
ATOM  3721 CZ  PHE  545      61.955  35.150  -6.480  1.00 31.01      C3
ATOM  3722 C   PHE  545      61.543  34.900  -1.667  1.00 34.81      C3
ATOM  3723 O   PHE  545      60.901  35.660  -2.389  1.00 38.88      C3
ATOM  3724 N   GLN  546      60.912  33.847  -1.135  1.00 34.77      C3
ATOM  3725 H   GLN  546      61.396  33.223  -0.558  1.00  0.00      C3
ATOM  3726 CA  GLN  546      59.490  33.637  -1.433  1.00 33.72      C3
ATOM  3727 CB  GLN  546      59.145  32.232  -1.140  1.00 34.85      C3
ATOM  3728 CG  GLN  546      59.582  31.585  -2.444  1.00 42.45      C3
ATOM  3729 CD  GLN  546      59.374  30.085  -2.473  1.00 46.05      C3
ATOM  3730 OE1 GLN  546      59.287  29.472  -1.399  1.00 48.90      C3
ATOM  3731 NE2 GLN  546      59.339  29.442  -3.644  1.00 47.20      C3
ATOM  3732 HE21 GLN  546      59.476  29.948  -4.472  1.00  0.00      C3
ATOM  3733 HE22 GLN  546      59.154  28.481  -3.609  1.00  0.00      C3
ATOM  3734 C   GLN  546      58.504  34.541  -0.729  1.00 31.62      C3
ATOM  3735 O   GLN  546      57.429  34.850  -1.233  1.00 29.88      C3
ATOM  3736 N   ARG  547      58.907  34.929   0.465  1.00 31.09      C3
ATOM  3737 H   ARG  547      59.750  34.566   0.811  1.00  0.00      C3
ATOM  3738 CA  ARG  547      58.160  35.830   1.282  1.00 31.43      C3
ATOM  3739 CB  ARG  547      58.813  35.874   2.601  1.00 31.74      C3
ATOM  3740 CG  ARG  547      57.906  35.224   3.623  1.00 37.02      C3
ATOM  3741 CD  ARG  547      58.344  33.858   4.076  1.00 40.56      C3
ATOM  3742 NE  ARG  547      59.743  34.058   4.345  1.00 47.90      C3
ATOM  3743 HE  ARG  547      60.389  33.924   3.620  1.00  0.00      C3
ATOM  3744 CZ  ARG  547      60.190  34.394   5.543  1.00 49.48      C3
ATOM  3745 NH1 ARG  547      59.361  34.522   6.593  1.00 51.97      C3
ATOM  3746 HH11 ARG  547      58.380  34.356   6.488  1.00  0.00      C3
ATOM  3747 HH12 ARG  547      59.731  34.763   7.491  1.00  0.00      C3
ATOM  3748 NH2 ARG  547      61.464  34.775   5.616  1.00 48.55      C3
ATOM  3749 HH21 ARG  547      62.025  34.803   4.788  1.00  0.00      C3
ATOM  3750 HH22 ARG  547      61.854  35.034   6.501  1.00  0.00      C3
ATOM  3751 C   ARG  547      58.167  37.181   0.590  1.00 32.26      C3
ATOM  3752 O   ARG  547      57.084  37.694   0.317  1.00 34.25      C3
ATOM  3753 N   ARG  548      59.348  37.717   0.205  1.00 31.44      C3
ATOM  3754 H   ARG  548      60.148  37.203   0.444  1.00  0.00      C3
ATOM  3755 CA  ARG  548      59.529  38.980  -0.555  1.00 30.01      C3
ATOM  3756 CB  ARG  548      60.995  39.213  -0.949  1.00 25.42      C3
ATOM  3757 CG  ARG  548      61.820  39.361   0.294  1.00 26.11      C3
ATOM  3758 CD  ARG  548      63.280  39.158  -0.054  1.00 29.34      C3
ATOM  3759 NE  ARG  548      64.044  39.162   1.189  1.00 32.30      C3
ATOM  3760 HE  ARG  548      63.572  38.883   1.995  1.00  0.00      C3
ATOM  3761 CZ  ARG  548      65.344  39.518   1.325  1.00 32.66      C3
ATOM  3762 NH1 ARG  548      66.159  39.923   0.335  1.00 34.98      C3
ATOM  3763 HH11 ARG  548      67.107  40.170   0.543  1.00  0.00      C3
ATOM  3764 HH12 ARG  548      65.812  39.981  -0.600  1.00  0.00      C3
ATOM  3765 NH2 ARG  548      65.837  39.518   2.549  1.00 32.03      C3
ATOM  3766 HH21 ARG  548      66.788  39.784   2.708  1.00  0.00      C3
ATOM  3767 HH22 ARG  548      65.250  39.275   3.327  1.00  0.00      C3
ATOM  3768 C   ARG  548      58.713  38.997  -1.832  1.00 29.81      C3
ATOM  3769 O   ARG  548      57.778  39.790  -1.968  1.00 33.03      C3
ATOM  3770 N   ALA  549      58.979  38.102  -2.761  1.00 27.87      C3
ATOM  3771 H   ALA  549      59.684  37.436  -2.601  1.00  0.00      C3
ATOM  3772 CA  ALA  549      58.227  38.045  -3.984  1.00 27.18      C3
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FIGURE 5

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ATOM  3773 CB  ALA  549      58.797  36.934  -4.857  1.00 28.72      C3
ATOM  3774 C   ALA  549      56.748  37.810  -3.770  1.00 25.91      C3
ATOM  3775 O   ALA  549      55.896  38.337  -4.468  1.00 26.03      C3
ATOM  3776 N   GLY  550      56.421  37.074  -2.748  1.00 26.53      C3
ATOM  3777 H   GLY  550      57.103  36.657  -2.185  1.00  0.00      C3
ATOM  3778 CA  GLY  550      55.055  36.805  -2.457  1.00 26.08      C3
ATOM  3779 C   GLY  550      54.410  38.098  -2.075  1.00 26.94      C3
ATOM  3780 O   GLY  550      53.339  38.380  -2.608  1.00 26.59      C3
ATOM  3781 N   GLY  551      55.073  38.917  -1.234  1.00 27.78      C3
ATOM  3782 H   GLY  551      55.958  38.642  -0.925  1.00  0.00      C3
ATOM  3783 CA  GLY  551      54.540  40.212  -0.779  1.00 26.51      C3
ATOM  3784 C   GLY  551      54.302  41.113  -1.994  1.00 26.82      C3
ATOM  3785 O   GLY  551      53.313  41.852  -2.065  1.00 27.82      C3
ATOM  3786 N   VAL  552      55.154  41.013  -3.012  1.00 25.81      C3
ATOM  3787 H   VAL  552      55.916  40.396  -2.954  1.00  0.00      C3
ATOM  3788 CA  VAL  552      54.952  41.843  -4.176  1.00 28.39      C3
ATOM  3789 CB  VAL  552      56.178  41.743  -5.190  1.00 26.20      C3
ATOM  3790 CG1 VAL  552      55.917  42.391  -6.541  1.00 26.53      C3
ATOM  3791 CG2 VAL  552      57.327  42.546  -4.594  1.00 26.44      C3
ATOM  3792 C   VAL  552      53.650  41.406  -4.820  1.00 29.05      C3
ATOM  3793 O   VAL  552      52.744  42.251  -4.888  1.00 31.68      C3
ATOM  3794 N   LEU  553      53.455  40.120  -5.176  1.00 27.20      C3
ATOM  3795 H   LEU  553      54.122  39.447  -4.908  1.00  0.00      C3
ATOM  3796 CA  LEU  553      52.266  39.705  -5.915  1.00 23.80      C3
ATOM  3797 CB  LEU  553      52.357  38.262  -6.363  1.00 24.86      C3
ATOM  3798 CG  LEU  553      53.432  37.955  -7.357  1.00 23.06      C3
ATOM  3799 CD1 LEU  553      54.073  36.623  -7.092  1.00 24.31      C3
ATOM  3800 CD2 LEU  553      52.794  38.061  -8.703  1.00 21.87      C3
ATOM  3801 C   LEU  553      51.012  39.825  -5.114  1.00 23.72      C3
ATOM  3802 O   LEU  553      49.982  40.138  -5.712  1.00 24.63      C3
ATOM  3803 N   VAL  554      50.962  39.580  -3.803  1.00 24.37      C3
ATOM  3804 H   VAL  554      51.774  39.350  -3.295  1.00  0.00      C3
ATOM  3805 CA  VAL  554      49.660  39.691  -3.180  1.00 26.36      C3
ATOM  3806 CB  VAL  554      49.472  38.751  -1.802  1.00 26.55      C3
ATOM  3807 CG1 VAL  554      50.696  37.933  -1.418  1.00 23.95      C3
ATOM  3808 CG2 VAL  554      48.953  39.614  -0.682  1.00 25.58      C3
ATOM  3809 C   VAL  554      49.322  41.175  -2.960  1.00 27.53      C3
ATOM  3810 O   VAL  554      48.142  41.502  -3.192  1.00 27.44      C3
ATOM  3811 N   ALA  555      50.277  42.106  -2.716  1.00 28.04      C3
ATOM  3812 H   ALA  555      51.221  41.831  -2.658  1.00  0.00      C3
ATOM  3813 CA  ALA  555      49.956  43.539  -2.509  1.00 28.57      C3
ATOM  3814 CB  ALA  555      51.161  44.427  -2.217  1.00 28.07      C3
ATOM  3815 C   ALA  555      49.402  44.055  -3.803  1.00 28.12      C3
ATOM  3816 O   ALA  555      48.425  44.803  -3.847  1.00 30.12      C3
ATOM  3817 N   SER  556      49.985  43.521  -4.839  1.00 26.44      C3
ATOM  3818 H   SER  556      50.781  42.956  -4.710  1.00  0.00      C3
ATOM  3819 CA  SER  556      49.548  43.810  -6.152  1.00 30.09      C3
ATOM  3820 CB  SER  556      50.684  43.277  -6.965  1.00 31.42      C3
ATOM  3821 OG  SER  556      50.442  43.338  -8.344  1.00 37.88      C3
ATOM  3822 HG  SER  556      49.966  44.144  -8.576  1.00  0.00      C3
ATOM  3823 C   SER  556      48.143  43.243  -6.454  1.00 32.78      C3
ATOM  3824 O   SER  556      47.287  43.961  -7.003  1.00 34.56      C3
ATOM  3825 N   HIS  557      47.750  42.019  -6.088  1.00 32.78      C3
ATOM  3826 H   HIS  557      48.350  41.453  -5.560  1.00  0.00      C3
ATOM  3827 CA  HIS  557      46.396  41.605  -6.401  1.00 33.64      C3
ATOM  3828 CB  HIS  557      46.203  40.142  -6.242  1.00 37.88      C3
ATOM  3829 CG  HIS  557      46.986  39.518  -7.348  1.00 42.44      C3
ATOM  3830 CD2 HIS  557      46.694  39.665  -8.675  1.00 43.63      C3
ATOM  3831 ND1 HIS  557      48.108  38.837  -7.209  1.00 45.23      C3
ATOM  3832 HD1 HIS  557      48.641  38.764  -6.385  1.00  0.00      C3
ATOM  3833 CE1 HIS  557      48.524  38.569  -8.414  1.00 46.56      C3
ATOM  3834 NE2 HIS  557      47.676  39.066  -9.283  1.00 45.62      C3
ATOM  3835 HE2 HIS  557      47.793  39.018 -10.257  1.00  0.00      C3
ATOM  3836 C   HIS  557      45.383  42.249  -5.520  1.00 32.94      C3
ATOM  3837 O   HIS  557      44.256  42.444  -5.934  1.00 33.08      C3
ATOM  3838 N   LEU  558      45.744  42.534  -4.280  1.00 33.05      C3
ATOM  3839 H   LEU  558      46.657  42.356  -3.986  1.00  0.00      C3
ATOM  3840 CA  LEU  558      44.817  43.125  -3.348  1.00 31.91      C3
ATOM  3841 CB  LEU  558      45.420  43.107  -1.965  1.00 29.25      C3
ATOM  3842 CG  LEU  558      44.605  43.615  -0.818  1.00 26.02      C3
ATOM  3843 CD1 LEU  558      43.279  42.883  -0.742  1.00 25.00      C3
ATOM  3844 CD2 LEU  558      45.496  43.571   0.408  1.00 22.86      C3
ATOM  3845 C   LEU  558      44.527  44.521  -3.783  1.00 32.47      C3
ATOM  3846 O   LEU  558      43.402  44.944  -3.596  1.00 33.97      C3
ATOM  3847 N   GLN  559      45.482  45.231  -4.370  1.00 34.36      C3
ATOM  3848 H   GLN  559      46.386  44.855  -4.406  1.00  0.00      C3
ATOM  3849 CA  GLN  559      45.255  46.569  -4.912  1.00 36.75      C3
ATOM  3850 CB  GLN  559      46.598  47.067  -5.470  1.00 39.63      C3
ATOM  3851 CG  GLN  559      46.707  48.543  -5.875  1.00 42.07      C3
ATOM  3852 CD  GLN  559      46.530  49.618  -4.793  1.00 41.53      C3
ATOM  3853 OE1 GLN  559      45.961  50.687  -5.057  1.00 41.25      C3
ATOM  3854 NE2 GLN  559      46.951  49.416  -3.561  1.00 37.96      C3
ATOM  3855 HE21 GLN  559      47.271  48.528  -3.311  1.00  0.00      C3
ATOM  3856 HE22 GLN  559      47.001  50.190  -2.967  1.00  0.00      C3
ATOM  3857 C   GLN  559      44.142  46.635  -5.976  1.00 35.22      C3
ATOM  3858 O   GLN  559      43.165  47.404  -5.839  1.00 34.99      C3
ATOM  3859 N   SER  560      44.260  45.817  -7.025  1.00 33.46      C3
ATOM  3860 H   SER  560      45.083  45.292  -7.154  1.00  0.00      C3
ATOM  3861 CA  SER  560      43.222  45.683  -8.049  1.00 32.88      C3
ATOM  3862 CB  SER  560      43.693  44.776  -9.088  1.00 34.05      C3
ATOM  3863 OG  SER  560      45.021  45.174  -9.281  1.00 42.40      C3
ATOM  3864 HG  SER  560      45.042  45.996  -9.783  1.00  0.00      C3
ATOM  3865 C   SER  560      41.885  45.133  -7.559  1.00 32.01      C3
ATOM  3866 O   SER  560      40.791  45.582  -7.920  1.00 32.23      C3
ATOM  3867 N   PHE  561      41.969  44.123  -6.710  1.00 29.50      C3
ATOM  3868 H   PHE  561      42.850  43.767  -6.464  1.00  0.00      C3
ATOM  3869 CA  PHE  561      40.803  43.529  -6.118  1.00 28.17      C3
ATOM  3870 CB  PHE  561      41.237  42.541  -5.040  1.00 26.27      C3
ATOM  3871 CG  PHE  561      40.069  41.966  -4.268  1.00 25.68      C3
ATOM  3872 CD1 PHE  561      39.282  40.999  -4.846  1.00 25.44      C3
ATOM  3873 CD2 PHE  561      39.761  42.482  -3.051  1.00 25.45      C3
ATOM  3874 CE1 PHE  561      38.166  40.551  -4.215  1.00 21.49      C3
```

FIGURE 5

```
ATOM  3875 CE2 PHE  561      38.635  42.027  -2.421  1.00 26.89      C3
ATOM  3876 CZ  PHE  561      37.853  41.074  -3.008  1.00 24.29      C3
ATOM  3877 C   PHE  561      39.987  44.645  -5.505  1.00 28.81      C3
ATOM  3878 O   PHE  561      38.789  44.697  -5.731  1.00 29.31      C3
ATOM  3879 N   LEU  562      40.672  45.565  -4.797  1.00 28.39      C3
ATOM  3880 H   LEU  562      41.643  45.462  -4.707  1.00  0.00      C3
ATOM  3881 CA  LEU  562      40.033  46.617  -4.057  1.00 26.51      C3
ATOM  3882 CB  LEU  562      40.964  47.203  -3.074  1.00 23.80      C3
ATOM  3883 CG  LEU  562      41.047  46.411  -1.816  1.00 24.85      C3
ATOM  3884 CD1 LEU  562      42.207  46.868  -1.049  1.00 24.07      C3
ATOM  3885 CD2 LEU  562      39.794  46.551  -1.008  1.00 25.13      C3
ATOM  3886 C   LEU  562      39.586  47.669  -4.988  1.00 29.27      C3
ATOM  3887 O   LEU  562      38.580  48.304  -4.681  1.00 29.83      C3
ATOM  3888 N   GLU  563      40.239  47.871  -6.115  1.00 30.88      C3
ATOM  3889 H   GLU  563      41.052  47.368  -6.325  1.00  0.00      C3
ATOM  3890 CA  GLU  563      39.738  48.908  -6.966  1.00 36.88      C3
ATOM  3891 CB  GLU  563      40.660  49.142  -8.137  1.00 40.80      C3
ATOM  3892 CG  GLU  563      41.999  49.628  -7.682  1.00 48.55      C3
ATOM  3893 CD  GLU  563      43.148  49.277  -8.619  1.00 55.42      C3
ATOM  3894 OE1 GLU  563      44.301  49.283  -8.135  1.00 57.39      C3
ATOM  3895 OE2 GLU  563      42.886  48.986  -9.808  1.00 56.44      C3
ATOM  3896 C   GLU  563      38.375  48.469  -7.466  1.00 39.02      C3
ATOM  3897 O   GLU  563      37.388  49.170  -7.270  1.00 39.09      C3
ATOM  3898 N   VAL  564      38.289  47.255  -8.030  1.00 42.30      C3
ATOM  3899 H   VAL  564      39.107  46.714  -8.074  1.00  0.00      C3
ATOM  3900 CA  VAL  564      37.052  46.683  -8.558  1.00 41.84      C3
ATOM  3901 CB  VAL  564      37.333  45.255  -9.041  1.00 42.27      C3
ATOM  3902 CG1 VAL  564      36.055  44.538  -9.435  1.00 41.17      C3
ATOM  3903 CG2 VAL  564      38.283  45.348 -10.241  1.00 42.11      C3
ATOM  3904 C   VAL  564      36.030  46.709  -7.442  1.00 41.68      C3
ATOM  3905 O   VAL  564      34.892  47.015  -7.697  1.00 42.34      C3
ATOM  3906 N   SER  565      36.419  46.501  -6.206  1.00 42.75      C3
ATOM  3907 H   SER  565      37.333  46.173  -6.063  1.00  0.00      C3
ATOM  3908 CA  SER  565      35.562  46.602  -5.064  1.00 44.85      C3
ATOM  3909 CB  SER  565      36.344  46.013  -3.894  1.00 46.54      C3
ATOM  3910 OG  SER  565      35.590  45.714  -2.731  1.00 51.75      C3
ATOM  3911 HG  SER  565      35.060  46.481  -2.491  1.00  0.00      C3
ATOM  3912 C   SER  565      35.167  48.063  -4.871  1.00 45.70      C3
ATOM  3913 O   SER  565      34.038  48.287  -4.446  1.00 46.87      C3
ATOM  3914 N   TYR  566      35.965  49.093  -5.146  1.00 47.59      C3
ATOM  3915 H   TYR  566      36.893  48.908  -5.386  1.00  0.00      C3
ATOM  3916 CA  TYR  566      35.518  50.474  -5.086  1.00 49.68      C3
ATOM  3917 CB  TYR  566      36.765  51.362  -5.164  1.00 56.17      C3
ATOM  3918 CG  TYR  566      36.715  52.622  -6.007  1.00 64.64      C3
ATOM  3919 CD1 TYR  566      37.264  52.538  -7.278  1.00 69.53      C3
ATOM  3920 CE1 TYR  566      37.212  53.613  -8.151  1.00 73.71      C3
ATOM  3921 CD2 TYR  566      36.109  53.797  -5.569  1.00 67.98      C3
ATOM  3922 CE2 TYR  566      36.048  54.888  -6.441  1.00 72.92      C3
ATOM  3923 CZ  TYR  566      36.599  54.787  -7.735  1.00 75.29      C3
ATOM  3924 OH  TYR  566      36.538  55.838  -8.652  1.00 77.42      C3
ATOM  3925 HH  TYR  566      36.905  55.565  -9.494  1.00  0.00      C3
ATOM  3926 C   TYR  566      34.524  50.696  -6.217  1.00 48.48      C3
ATOM  3927 O   TYR  566      33.545  51.376  -5.950  1.00 46.35      C3
ATOM  3928 N   ALA  567      34.679  50.115  -7.417  1.00 49.14      C3
ATOM  3929 H   ALA  567      35.512  49.625  -7.572  1.00  0.00      C3
ATOM  3930 CA  ALA  567      33.670  50.165  -8.490  1.00 52.09      C3
ATOM  3931 CB  ALA  567      34.210  49.574  -9.788  1.00 48.37      C3
ATOM  3932 C   ALA  567      32.315  49.449  -8.238  1.00 55.31      C3
ATOM  3933 O   ALA  567      31.226  50.008  -8.501  1.00 56.87      C3
ATOM  3934 N   VAL  568      32.247  48.211  -7.736  1.00 57.66      C3
ATOM  3935 H   VAL  568      33.083  47.729  -7.564  1.00  0.00      C3
ATOM  3936 CA  VAL  568      30.980  47.573  -7.490  1.00 59.61      C3
ATOM  3937 CB  VAL  568      31.119  46.031  -7.339  1.00 58.96      C3
ATOM  3938 CG1 VAL  568      31.239  45.508  -5.911  1.00 60.27      C3
ATOM  3939 CG2 VAL  568      29.851  45.471  -7.922  1.00 60.44      C3
ATOM  3940 C   VAL  568      30.393  48.177  -6.245  1.00 62.66      C3
ATOM  3941 O   VAL  568      29.174  48.154  -6.180  1.00 64.78      C3
ATOM  3942 N   LEU  569      31.075  48.737  -5.248  1.00 66.15      C3
ATOM  3943 H   LEU  569      32.058  48.719  -5.243  1.00  0.00      C3
ATOM  3944 CA  LEU  569      30.359  49.334  -4.123  1.00 69.85      C3
ATOM  3945 CB  LEU  569      31.285  49.858  -3.023  1.00 69.91      C3
ATOM  3946 CG  LEU  569      32.007  48.887  -2.095  1.00 70.17      C3
ATOM  3947 CD1 LEU  569      32.847  49.687  -1.140  1.00 70.19      C3
ATOM  3948 CD2 LEU  569      31.039  48.054  -1.286  1.00 70.56      C3
ATOM  3949 C   LEU  569      29.567  50.509  -4.667  1.00 72.69      C3
ATOM  3950 O   LEU  569      28.365  50.553  -4.425  1.00 73.80      C3
ATOM  3951 N   ARG  570      30.180  51.391  -5.479  1.00 75.95      C3
ATOM  3952 H   ARG  570      31.153  51.299  -5.580  1.00  0.00      C3
ATOM  3953 CA  ARG  570      29.510  52.498  -6.173  1.00 78.78      C3
ATOM  3954 CB  ARG  570      30.399  53.068  -7.308  1.00 80.07      C3
ATOM  3955 CG  ARG  570      29.658  54.222  -7.997  1.00 84.16      C3
ATOM  3956 CD  ARG  570      29.976  54.744  -9.417  1.00 85.66      C3
ATOM  3957 NE  ARG  570      28.892  55.690  -9.737  1.00 85.67      C3
ATOM  3958 HE  ARG  570      27.971  55.354  -9.727  1.00  0.00      C3
ATOM  3959 CZ  ARG  570      29.051  56.991 -10.026  1.00 85.06      C3
ATOM  3960 NH1 ARG  570      30.240  57.590 -10.082  1.00 84.43      C3
ATOM  3961 HH11 ARG  570      31.069  57.056  -9.908  1.00  0.00      C3
ATOM  3962 HH12 ARG  570      30.295  58.561 -10.314  1.00  0.00      C3
ATOM  3963 NH2 ARG  570      27.958  57.736 -10.154  1.00 84.57      C3
ATOM  3964 HH21 ARG  570      27.059  57.316 -10.030  1.00  0.00      C3
ATOM  3965 HH22 ARG  570      28.042  58.708 -10.375  1.00  0.00      C3
ATOM  3966 C   ARG  570      28.201  52.009  -6.812  1.00 79.92      C3
ATOM  3967 O   ARG  570      27.107  52.565  -6.709  1.00 79.61      C3
ATOM  3968 N   HIS  571      28.362  50.900  -7.511  1.00 81.35      C3
ATOM  3969 H   HIS  571      29.214  50.417  -7.440  1.00  0.00      C3
ATOM  3970 CA  HIS  571      27.247  50.406  -8.197  1.00 82.75      C3
ATOM  3971 CB  HIS  571      27.882  49.274  -9.167  1.00 83.42      C3
ATOM  3972 CG  HIS  571      28.633  50.029 -10.280  1.00 85.08      C3
ATOM  3973 CD2 HIS  571      28.921  49.529 -11.532  1.00 85.81      C3
ATOM  3974 ND1 HIS  571      29.074  51.303 -10.268  1.00 86.25      C3
ATOM  3975 HD1 HIS  571      29.080  51.900  -9.489  1.00  0.00      C3
ATOM  3976 CE1 HIS  571      29.595  51.595 -11.459  1.00 86.01      C3
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FIGURE 5

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ATOM  3977 NE2 HIS  571      29.494  50.518 -12.187  1.00 86.28      C3
ATOM  3978 HE2 HIS  571      29.801  50.468 -13.119  1.00  0.00      C3
ATOM  3979 C   HIS  571      26.225  49.759  -7.195  1.00 83.31      C3
ATOM  3980 O   HIS  571      25.075  50.194  -7.301  1.00 84.06      C3
ATOM  3981 N   LEU  572      26.540  48.963  -6.158  1.00 83.11      C3
ATOM  3982 H   LEU  572      27.474  48.824  -5.915  1.00  0.00      C3
ATOM  3983 CA  LEU  572      25.527  48.457  -5.241  1.00 83.71      C3
ATOM  3984 CB  LEU  572      26.085  47.267  -4.454  1.00 83.57      C3
ATOM  3985 CG  LEU  572      25.439  45.884  -4.721  1.00 83.79      C3
ATOM  3986 CD1 LEU  572      25.783  45.386  -6.127  1.00 84.16      C3
ATOM  3987 CD2 LEU  572      25.958  44.866  -3.714  1.00 84.08      C3
ATOM  3988 C   LEU  572      24.997  49.511  -4.261  1.00 84.78      C3
ATOM  3989 O   LEU  572      24.265  49.192  -3.295  1.00 84.85      C3
ATOM  3990 N   ALA  573      25.349  50.796  -4.483  1.00 85.56      C3
ATOM  3991 H   ALA  573      26.020  50.980  -5.174  1.00  0.00      C3
ATOM  3992 CA  ALA  573      24.822  51.925  -3.721  1.00 85.90      C3
ATOM  3993 CB  ALA  573      25.600  53.207  -3.970  1.00 85.79      C3
ATOM  3994 C   ALA  573      23.373  52.245  -4.057  1.00 87.21      C3
ATOM  3995 OT1 ALA  573      22.610  52.413  -3.099  1.00 88.33      C3
ATOM  3996 OT2 ALA  573      23.022  52.309  -5.248  1.00 88.34      C3
ATOM  3997 OH2 H2O  603      26.735  24.280   5.161  1.00 27.42      W
ATOM  3998 H1  H2O  603      27.332  24.335   4.407  1.00  0.00      W
ATOM  3999 H2  H2O  603      26.288  23.435   4.992  1.00  0.00      W
ATOM  4000 OH2 H2O  605      47.880  37.960  12.073  1.00 56.30      W
ATOM  4001 H1  H2O  605      47.789  37.874  13.031  1.00  0.00      W
ATOM  4002 H2  H2O  605      46.980  37.858  11.753  1.00  0.00      W
ATOM  4003 OH2 H2O  607      40.001  49.224   7.214  1.00 40.04      W
ATOM  4004 H1  H2O  607      40.471  48.761   7.909  1.00  0.00      W
ATOM  4005 H2  H2O  607      40.123  48.642   6.457  1.00  0.00      W
ATOM  4006 OH2 H2O  610      59.883  42.530  -9.698  1.00 38.90      W
ATOM  4007 H1  H2O  610      60.512  41.833  -9.477  1.00  0.00      W
ATOM  4008 H2  H2O  610      59.189  42.046 -10.160  1.00  0.00      W
ATOM  4009 OH2 H2O  611      57.178  35.940 -14.220  1.00 34.63      W
ATOM  4010 H1  H2O  611      57.174  36.545 -14.974  1.00  0.00      W
ATOM  4011 H2  H2O  611      57.989  36.211 -13.757  1.00  0.00      W
ATOM  4012 OH2 H2O  612      25.793  27.337  19.130  1.00 29.21      W
ATOM  4013 H1  H2O  612      26.709  27.661  19.145  1.00  0.00      W
ATOM  4014 H2  H2O  612      25.762  26.792  19.929  1.00  0.00      W
ATOM  4015 OH2 H2O  615      29.766  34.284   9.444  1.00 45.03      W
ATOM  4016 H1  H2O  615      30.017  34.618  10.308  1.00  0.00      W
ATOM  4017 H2  H2O  615      29.113  33.592   9.660  1.00  0.00      W
ATOM  4018 OH2 H2O  617      37.316  40.012  10.872  1.00 35.21      W
ATOM  4019 H1  H2O  617      36.600  40.017  11.519  1.00  0.00      W
ATOM  4020 H2  H2O  617      37.944  39.376  11.259  1.00  0.00      W
ATOM  4021 OH2 H2O  619      40.370  52.041  -7.387  1.00 29.62      W
ATOM  4022 H1  H2O  619      40.672  52.724  -6.779  1.00  0.00      W
ATOM  4023 H2  H2O  619      39.505  51.810  -7.052  1.00  0.00      W
ATOM  4024 OH2 H2O  621      27.903  32.440  10.664  1.00 39.99      W
ATOM  4025 H1  H2O  621      27.553  33.207  11.141  1.00  0.00      W
ATOM  4026 H2  H2O  621      27.929  31.808  11.398  1.00  0.00      W
ATOM  4027 OH2 H2O  622      25.057  31.972  13.675  1.00 32.70      W
ATOM  4028 H1  H2O  622      24.393  32.417  14.215  1.00  0.00      W
ATOM  4029 H2  H2O  622      24.469  31.428  13.112  1.00  0.00      W
ATOM  4030 OH2 H2O  623      20.791  28.583  14.218  1.00 50.17      W
ATOM  4031 H1  H2O  623      20.499  28.803  13.325  1.00  0.00      W
ATOM  4032 H2  H2O  623      19.939  28.549  14.688  1.00  0.00      W
ATOM  4033 OH2 H2O  625      22.680  78.881   2.761  1.00 40.48      W
ATOM  4034 H1  H2O  625      21.938  78.856   3.375  1.00  0.00      W
ATOM  4035 H2  H2O  625      22.266  79.246   1.970  1.00  0.00      W
ATOM  4036 OH2 H2O  626      39.689  36.486   9.730  1.00 23.36      W
ATOM  4037 H1  H2O  626      39.090  35.724   9.672  1.00  0.00      W
ATOM  4038 H2  H2O  626      39.627  36.872   8.853  1.00  0.00      W
ATOM  4039 OH2 H2O  627      42.035  78.320   5.697  1.00 46.19      W
ATOM  4040 H1  H2O  627      42.416  77.450   5.832  1.00  0.00      W
ATOM  4041 H2  H2O  627      41.243  78.146   5.181  1.00  0.00      W
ATOM  4042 OH2 H2O  631      47.227  31.440   6.299  1.00 34.17      W
ATOM  4043 H1  H2O  631      47.533  32.209   5.809  1.00  0.00      W
ATOM  4044 H2  H2O  631      47.442  30.713   5.714  1.00  0.00      W
ATOM  4045 OH2 H2O  636      24.043  65.423  -0.336  1.00 73.38      W
ATOM  4046 H1  H2O  636      24.179  65.781  -1.228  1.00  0.00      W
ATOM  4047 H2  H2O  636      23.469  66.096   0.054  1.00  0.00      W
ATOM  4048 OH2 H2O  638      38.984  67.955 -11.226  1.00 29.97      W
ATOM  4049 H1  H2O  638      38.283  67.402 -11.580  1.00  0.00      W
ATOM  4050 H2  H2O  638      39.568  68.046 -11.998  1.00  0.00      W
ATOM  4051 OH2 H2O  639      27.930  66.675  -7.733  1.00 43.40      W
ATOM  4052 H1  H2O  639      28.192  67.028  -6.876  1.00  0.00      W
ATOM  4053 H2  H2O  639      26.975  66.791  -7.705  1.00  0.00      W
ATOM  4054 OH2 H2O  643      50.619  62.802   0.813  1.00 36.55      W
ATOM  4055 H1  H2O  643      51.575  62.904   0.824  1.00  0.00      W
ATOM  4056 H2  H2O  643      50.301  63.665   0.525  1.00  0.00      W
ATOM  4057 OH2 H2O  646      62.897  38.367   3.759  1.00 73.55      W
ATOM  4058 H1  H2O  646      62.414  38.098   2.978  1.00  0.00      W
ATOM  4059 H2  H2O  646      62.244  38.247   4.461  1.00  0.00      W
ATOM  4060 OH2 H2O  650      29.587  68.480  -9.555  1.00 65.67      W
ATOM  4061 H1  H2O  650      28.846  68.630 -10.148  1.00  0.00      W
ATOM  4062 H2  H2O  650      29.180  67.844  -8.936  1.00  0.00      W
ATOM  4063 OH2 H2O  652      51.408  56.331   4.056  1.00 62.90      W
ATOM  4064 H1  H2O  652      50.718  56.353   3.365  1.00  0.00      W
ATOM  4065 H2  H2O  652      51.052  55.671   4.648  1.00  0.00      W
ATOM  4066 OH2 H2O  653      49.404  56.022   2.161  1.00 51.28      W
ATOM  4067 H1  H2O  653      49.442  55.351   1.474  1.00  0.00      W
ATOM  4068 H2  H2O  653      49.323  56.829   1.630  1.00  0.00      W
ATOM  4069 OH2 H2O  654      68.215  42.294  -2.563  1.00 40.77      W
ATOM  4070 H1  H2O  654      68.347  41.745  -1.777  1.00  0.00      W
ATOM  4071 H2  H2O  654      68.189  43.181  -2.190  1.00  0.00      W
ATOM  4072 OH2 H2O  655      66.374  40.425  -2.489  1.00 42.31      W
ATOM  4073 H1  H2O  655      66.936  41.162  -2.766  1.00  0.00      W
ATOM  4074 H2  H2O  655      66.452  39.841  -3.252  1.00  0.00      W
ATOM  4075 OH2 H2O  656      66.927  41.428  -5.011  1.00 44.08      W
ATOM  4076 H1  H2O  656      66.207  42.071  -4.989  1.00  0.00      W
ATOM  4077 H2  H2O  656      67.542  41.824  -4.474  1.00  0.00      W
ATOM  4078 OH2 H2O  657      40.371  57.111   5.730  1.00 66.56      W
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FIGURE 5

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ATOM  4079 H1  H2O  657    39.958 56.259  5.613 1.00 0.00    W
ATOM  4080 H2  H2O  657    40.021 57.651  5.014 1.00 0.00    W
ATOM  4081 OH2 H2O  658    48.780 47.580 -3.122 1.00 52.09   W
ATOM  4082 H1  H2O  658    48.811 46.671 -3.438 1.00 0.00    W
ATOM  4083 H2  H2O  658    49.568 47.955 -3.542 1.00 0.00    W
ATOM  4084 OH2 H2O  663    29.095 62.889  1.825 1.00 39.23   W
ATOM  4085 H1  H2O  663    29.380 62.827  2.739 1.00 0.00    W
ATOM  4086 H2  H2O  663    28.377 63.526  1.887 1.00 0.00    W
ATOM  4087 OH2 H2O  664    27.132 25.640  7.430 1.00 50.65   W
ATOM  4088 H1  H2O  664    26.870 24.838  7.876 1.00 0.00    W
ATOM  4089 H2  H2O  664    27.001 25.362  6.496 1.00 0.00    W
ATOM  4090 OH2 H2O  665    23.367 30.554 12.167 1.00 49.69   W
ATOM  4091 H1  H2O  665    24.026 30.006 11.707 1.00 0.00    W
ATOM  4092 H2  H2O  665    22.941 31.016 11.438 1.00 0.00    W
ATOM  4093 OH2 H2O  666    46.015 32.192 10.179 1.00 66.86   W
ATOM  4094 H1  H2O  666    46.060 31.519  9.497 1.00 0.00    W
ATOM  4095 H2  H2O  666    45.411 31.827 10.833 1.00 0.00    W
ATOM  4096 OH2 H2O  667    38.943 37.883 11.978 1.00 47.87   W
ATOM  4097 H1  H2O  667    39.367 37.487 11.188 1.00 0.00    W
ATOM  4098 H2  H2O  667    38.521 37.114 12.362 1.00 0.00    W
ATOM  4099 OH2 H2O  671    33.437 58.101  2.269 1.00 46.65   W
ATOM  4100 H1  H2O  671    33.555 57.162  2.433 1.00 0.00    W
ATOM  4101 H2  H2O  671    33.962 58.514  2.961 1.00 0.00    W
ATOM  4102 OH2 H2O  672    27.551 31.314 20.022 1.00 30.15   W
ATOM  4103 H1  H2O  672    27.929 32.042 20.533 1.00 0.00    W
ATOM  4104 H2  H2O  672    26.845 31.764 19.552 1.00 0.00    W
ATOM  4105 OH2 H2O  673    25.714 36.908 21.385 1.00 36.95   W
ATOM  4106 H1  H2O  673    24.806 37.123 21.637 1.00 0.00    W
ATOM  4107 H2  H2O  673    25.599 36.284 20.654 1.00 0.00    W
ATOM  4108 OH2 H2O  674    38.244 66.897 12.076 1.00 57.36   W
ATOM  4109 H1  H2O  674    37.773 67.536 12.626 1.00 0.00    W
ATOM  4110 H2  H2O  674    38.153 66.104 12.618 1.00 0.00    W
ATOM  4111 OH2 H2O  675    35.762 36.553 -3.986 1.00 58.40   W
ATOM  4112 H1  H2O  675    35.600 37.449 -3.677 1.00 0.00    W
ATOM  4113 H2  H2O  675    35.549 36.642 -4.923 1.00 0.00    W
ATOM  4114 OH2 H2O  676    30.689 32.814 25.675 1.00 59.30   W
ATOM  4115 H1  H2O  676    30.093 33.571 25.680 1.00 0.00    W
ATOM  4116 H2  H2O  676    31.550 33.214 25.540 1.00 0.00    W
END
```

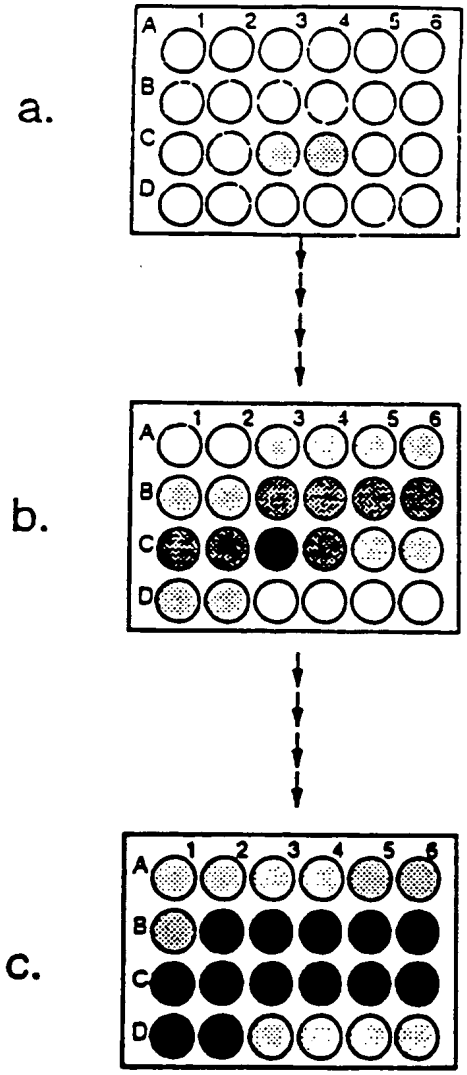

FIGURE 6

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EUROPEAN SEARCH REPORT

Application Number
EP 94 10 1207

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.5)
P,X	DISSERTATION ABSTRACTS INTERNATIONAL B. vol. 54, no. 3 , September 1993 page 1239 T. OSSLUND ET AL 'The structure of granulocyte-colony stimulating factor' * abstract *	1-8	C12N15/27 C07K3/00 C12P21/02 C07K13/00 G06F15/60
P,X	PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF USA vol. 90 , June 1993 , WASHINGTON US pages 5167 - 5171 C.P. HILL ET AL 'The structure of Granulocyte-colony-stimulating factor and its relationship to other growth factors' * the whole document *	1-8	
X	CELL STRUCTURE AND FUNCTION vol. 17, no. 1 , February 1992 pages 61 - 65 MASAHARU ISHIKAWA ET AL 'The sustitution of Cysteine 17 of recombinant human G-CSF with Alanine greatly enhanced its stability' * the whole document *	43	
X D	WO-A-87 01132 (KIRIN-AMGEN, INC.) * claims; examples 7-9 * & US-A-4 810 643 (KIRIN AMGEN , INC.) 7 March 1989	9	
X D	WO-A-89 05824 (GENETICS INSTITUTE, INC.) * the whole document especially page 17 table 2 , page 21 lines 16-19 and page 22 lines 25-37 * & US-A-4 904 584 (GENETICS INSTITUTE)	17-22	
	-/--		

TECHNICAL FIELDS SEARCHED (Int.Cl.5)
C12N
C07K
C12P

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	11 May 1994	Le Cornec, N

CATEGORY OF CITED DOCUMENTS

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Application Number
EP 94 10 1207

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.5)
A,D	BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS vol. 159, no. 1 , 28 February 1989 , DULUTH, MINNESOTA US pages 103 - 111 TETSURO KUGA ET AL 'Mutagenesis of human granulocyte colony stimulating factor' * the whole document * ---	9-60	
D,Y	EP-A-0 344 796 (CHUGAI SEIYAKU KABUSHIKI KAISHA) * the whole document * ---	1-8	
Y	BIOCHEMISTRY vol. 30 , 1991 , EASTON, PA US pages 4151 - 4159 L. ABRAHMSEN ET AL 'Engineering subtilisin and its sustrates for efficient ligation of peptide bonds in aqueous solution' * the whole document especially page 4152 right column , page 4153 right column and the discussion * ---	1-8	TECHNICAL FIELDS SEARCHED (Int.Cl.5)
Y,D	SCIENCE vol. 258 , 20 November 1992 , LANCASTER, PA US pages 1358 - 1362 J. PANDIT ET AL 'Three-dimensional Structure of dimeric human recombinant Macrophage Colony-Stimulating Factor' * the whole document * ---	1-8	
P,A	WO-A-93 25687 (CHIRON CORPORATION) * page 16, line 11 - page 17, line 5 * * examples 1,9,10,11,13 * * appendix 1 * * claims * --- -/--	1-8	

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	11 May 1994	Le Cornec, N

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Application Number
EP 94 10 1207

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.5)
P,X	JOURNAL OF CELLULAR BIOCHEMISTRY SUPPL 0 no. 17B , 26 JANUARY-10 FEBRUARY 1993 page 78 J. E. LAYTON ET AL 'Interaction of G-CSF with its receptor : Dissociation of biological activity and Receptor binding' * abstract E 225 *	27,32, 34-38, 51-53	
A	EP-A-0 456 200 (BOEHRINGER MANNHEIM GMBH)		
D,A	JOURNAL OF APPLIED CRYSTALLOGRAPHY vol. 20 , 1987 pages 366 - 373 M.J. COX ET AL 'Experiments with automated protein crystallization'		
T	POUR LA SCIENCE vol. 183 , January 1993 pages 76 - 82 A. OLSON ET AL 'Voir les Molécules biologiques'		TECHNICAL FIELDS SEARCHED (Int.Cl.5)
Y	PROTEIN ENGINEERING 1987 , ALAN R. LISS, INC. pages 35 - 44 M. KARPLUS 'The prediction and Analysis of mutant strutures' * the whole document *	1-8	
A	WO-A-88 01775 (GENEX CORPORATION) 10 March 1988		

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	11 May 1994	Le Cornec, N

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X : particularly relevant if taken alone
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